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<b>(54) Title:</b> HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAS ENCODING THESE PROTEINS  <b>(57) Abstract</b>  A human protein having a hydrophobic domain and comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10, a cDNA coding for said protein, and an expression vector comprising the cDNA as well as an eucaryotic cell comprising the cDNA. The protein can be provided by expression of the cDNA coding for such protein.		

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## DESCRIPTION

HUMAN PROTEINS HAVING HYDROPHOBIC  
DOMAINS AND DNAs ENCODING THESE PROTEINS

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TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as eucaryotic cells expressing these DNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against these proteins. The human cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by these cDNAs. Cells, wherein these membrane protein genes are introduced to express secretory proteins and membrane proteins in large amounts, can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular pharmaceuticals, and so on.

BACKGROUND ART

Cells secrete many proteins outside the cells. These secretory proteins play important roles for the proliferation control, the differentiation induction, the material transportation, the biological protection, etc. in the cells. Different from intracellular proteins, the secretory proteins exert their actions outside the cells, whereby they can be administered in the intracorporeal manner such as the injection or the drip, so that there

are hidden potentialities as medicines. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents, etc. have been currently employed as medicines. In addition, secretory proteins other than those described above have been undergoing clinical trials to develop as pharmaceuticals. Because it has been conceived that the human cells still produce many unknown secretory proteins, availability of these secretory proteins as well as genes coding for them is expected to lead to development of novel pharmaceuticals utilizing these proteins.

On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. in the material transportation and the information transmission which are mediated by the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino acids, and so on, where the genes of many of them have been cloned already. It has been clarified that abnormalities of these membrane proteins are associated with a number of hitherto-cryptogenic diseases. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification, these secretory proteins and membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises transfection of a cDNA library in eucaryotic cells to express cDNAs and then screening of the cells expressing

the target active protein by secretion or on the surface of membrane. However, this method is applicable only to cloning of a gene of a protein with a known function.

In general, secretory proteins and membrane proteins possess at least one hydrophobic domain inside the proteins, wherein, after synthesis thereof in the ribosome, this domain works as a secretory signal or remains in the phospholipid membrane to be trapped in the membrane. Accordingly, the evidence of this cDNA for encoding the secretory proteins and the membrane protein is provided by determination of the whole base sequence of a full-length cDNA followed by detection of highly hydrophobic domains in the amino acid sequence of the protein encoded by this cDNA.

#### DISCLOSURE OF INVENTION

The object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as transformation eucaryotic cells that are capable of expressing these DNAs.

As the result of intensive studies, the present inventors have been successful in cloning of cDNAs coding for proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. In other words, the present invention provides human proteins having hydrophobic domains, namely proteins containing any of the amino acid sequences represented by Sequence Nos. 1 to 10. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs containing any of the base sequences represented by Sequence Nos. 11 to 21, 23, 25, 27, 29, 31,

33, 35, 37 and 39, as well as expression vectors that are capable of expressing any of these DNAs by in vitro translation or in eucaryotic cells and transformation eucaryotic cells that are capable of expressing these DNAs and of producing the above-mentioned proteins.

#### BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP00631.

Fig. 2 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02403.

Fig. 3 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02420.

Fig. 4 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10349.

Fig. 5 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10508.

Fig. 6 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10524.

Fig. 7 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10529.

Fig. 8 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10537.

Fig. 9 A figure depicting the

hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10549.

Fig. 10 A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10551.

#### BEST MODE FOR CARRYING OUT THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the hydrophobic domains of the present invention, wherein the method for obtainment by the recombinant DNA technology is employed preferably. For instance, in vitro expression of the proteins can be achieved by preparation of an RNA by in vitro transcription from a vector having one of cDNAs of the present invention, followed by in vitro translation using this RNA as a template. Also, recombination of the translation region into a suitable expression vector by the method known in the art leads to expression of a large amount of the encoded protein by using prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case in which one of the proteins of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro, when the translation region of this cDNA is subjected to recombination to a vector having an RNA polymerase promoter, followed by addition to an in vitro translation system such as a rabbit reticulocyte

lysate or a wheat germ extract, containing an RNA polymerase corresponding to the promoter. RNA polymerase inhibitors are exemplified by T7, T3, SP6, and the like. The vectors containing these RNA polymerase inhibitors are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II, and so on. Furthermore, a membrane protein of the present invention can be expressed as the form incorporated in the microsome membrane, when a canine pancreas microsome or the like is added into the reaction system.

In the case in which a protein of the present invention is produced by expressing the DNA using a microorganism such as *Escherichia coli* etc., a recombinant expression vector bearing the translation region in the cDNA of the present invention is constructed in an expression vector having an origin, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator etc., which can be replicated in the microorganism, and, after transformation of the host cells with this expression vector, the thus-obtained transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the microorganism. In this case, a protein fragment containing an optional region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind an optional translation region. Alternatively, a fusion protein with another protein can be expressed. Only a protein portion coding for this cDNA can be obtained by cleavage of this fusion protein with a suitable protease. The expression vector for *Escherichia coli* is exemplified by the pUC system, pBluescript II, the pET expression system, the pGEX expression system, and so

on.

In the case in which one of the proteins of the present invention is produced by expressing the DNA in eucaryotic cells, the protein of the present invention can be obtained by secretory production or produced as a membrane protein on the cell-membrane surface, when the translation region of this cDNA is subjected to recombination to an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) insertion site, etc., followed by introduction into the eucaryotic cells. The expression vector is exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian culture cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, etc., budding yeasts, fission yeasts, silkworm cells, *Xenopus laevis* egg cells, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the present proteins. The expression vector can be introduced in the eucaryotic cells by methods known in the art such as the electroporation method, the potassium phosphate method, the liposome method, the DEAE-dextran method, and so on.

After one of the proteins of the present invention is expressed in prokaryotic cells or eucaryotic cells, the objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea or a surface-active agent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-

exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

5 The proteins of the present invention include peptide fragments (more than 5 amino acid residues) containing any partial amino acid sequence in the amino acid sequences represented by Sequence Nos. 1. to 10. These peptide fragments can be utilized as antigens for preparation of antibodies. Hereupon, among the proteins of the present  
10 invention, those having the signal sequence are secreted in the form of maturation proteins on the surface of the cells, after the signal sequences are removed. Therefore, these maturation proteins shall come within the scope of the present invention. The N-terminal amino acid sequences  
15 of the maturation proteins can be easily identified by using the method for the cleavage-site determination in a signal sequence [Japanese Patent Kokai Publication No. 1996-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the  
20 secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins wherein  
25 sugar chains are added. Accordingly, such proteins or peptides wherein sugar chains are added shall come within the scope of the present invention.

The DNAs of the present invention include all DNAs coding for the above-mentioned proteins. These DNAs can be  
30 obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for

example, from cDNA libraries of the human cell origin. These cDNA are synthesized by using as templates poly(A)<sup>+</sup> RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the culture cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available, human cDNA libraries can be utilized. Cloning of the cDNAs of the present invention from the cDNA libraries can be carried out by synthesis of an oligonucleotide on the basis of an optional portion in the cDNA base sequences of the present invention, followed by screening using this oligonucleotide as the probe according to the colony or plaque hybridization by a method known in the art. In addition, the cDNA fragments of the present invention can be prepared by synthesis of an oligonucleotide to be hybridized at both termini of the objective cDNA fragment, followed by the usage of this oligonucleotide as the primer for the RT-PCR method from an mRNA isolated from human cells.

The cDNAs of the present invention are characterized by containing either of the base sequences represented by Sequence Nos. 11 to 20 or the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Table 1 summarizes the clone number (HP number), the cells affording the cDNA, the total base number of the cDNA, and the number of the amino acid residues of the encoded

protein, for each of the cDNAs.

Table 1

Sequence No.	HP number	Cells	Base number	Number of amino acid residues
1, 11, 21	HP00631	Saos-2	1085	238
2, 12, 23	HP02403	Stomach cancer	1168	194
3, 13, 25	HP02420	Stomach cancer	624	139
4, 14, 27	HP10349	Stomach cancer	1121	323
5, 15, 29	HP10508	Stomach cancer	827	231
6, 16, 31	HP10524	Stomach cancer	1189	97
7, 17, 33	HP10529	Saos-2	1500	198
8, 18, 35	HP10537	Saos-2	806	140
9, 19, 37	HP10549	Stomach cancer	1718	201
10, 20, 39	HP10551	Stomach cancer	995	249

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Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines and human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39.

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In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA that is subjected to insertion or deletion of one or plural nucleotides and/or substitution with other nucleotides in Sequence Nos. 11 to 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39 shall come within the scope of the present invention.

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In a similar manner, any protein that is formed by these modifications comprising insertion or deletion of one or plural amino acids and/or substitution with other amino acids shall come within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by Sequence Nos. 1 to 10.

The cDNAs of the present invention include cDNA fragments (more than 10 bp) containing any partial base sequence in the base sequences represented by Sequence Nos. 11 to 20 or in the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39. Also, DNA fragments consisting of a sense chain and an anti-sense chain shall come within this scope. These DNA fragments can be utilized as the probes for the gene diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

#### Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a

particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the

corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands.

5 Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved  
10 in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for  
15 commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor  
20 Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

#### Nutritional Uses

25 Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In  
30 such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation,

such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular

Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon  $\gamma$ , Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C.

and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

5 Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

#### Immune Stimulating or Suppressing Activity

20 A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., 25 in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or 30 may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or

other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-

specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by

immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate

disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from

the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I  $\alpha$  chain protein and  $\beta_2$  microglobulin protein or an MHC class II $\alpha$  chain protein and an MHC class II $\beta$  chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan,

A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans);  
5 Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl.  
10 Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al.,  
15 Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without  
20 limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds.  
25 Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without  
30 limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro

assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

5           Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 10           1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of 15           Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

          Assays for lymphocyte survival/apoptosis (which will 20           identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca 25           et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

30           Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood

84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

5 A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates  
10 involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with  
15 irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with  
20 chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use  
25 in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell  
30 disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well

as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc.,

New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

#### Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of

bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be

useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or

regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

#### Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin  $\alpha$  family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- $\beta$  group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

#### Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those

described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

#### Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

#### Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or

inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their  
5 ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of  
10 cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of  
15 receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include  
20 without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions  
25 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670,  
30 1995.

#### Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

#### Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by

inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

5        Other Activities

         A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, 10 viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast 15 augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, 20 protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and 25 violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme 30 and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example,

psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

#### Examples

The present invention is embodied in more detail by the following examples, but this embodiment is not intended to restrict the present invention. The basic operations and the enzyme reactions with regard to the DNA recombination are carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from TAKARA SHUZO. The manufacturer's instructions were used for the buffer compositions as well as for the reaction conditions, in each of the enzyme reactions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

#### (1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

cDNA libraries (WO97/33993) of osteosarcoma cell line Saos-2 and cDNA libraries (WO97/15596) of tissues of stomach cancer delivered by the operation were used for the cDNA libraries. Full-length cDNA clones were selected from respective libraries and the whole base sequences thereof were determined to construct a homo/protein cDNA bank consisting of the full-length cDNA clones. The

hydrophobicity/hydrophilicity profiles were obtained for proteins encoded by the full-length cDNA clones registered in the homo/protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. Any clone that has a hydrophobic region being putative as a secretory signal or a transmembrane domain in the amino acid sequence of an encoded protein was selected as a clone candidate.

#### 10 (2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T<sub>N</sub>T rabbit reticulocyte lysate kit (Promega). In this case, [<sup>35</sup>S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was reacted at 30°C for 90 minutes in a total 25 µl volume of the reaction solution containing 12.5 µl of T<sub>N</sub>T rabbit reticulocyte lysate, 0.5 µl of a buffer solution (attached to kit), 2 µl of an amino acid mixture (methionine-free), 2 µl of [<sup>35</sup>S]methionine (Amersham) (0.37 MBq/µl), 0.5 µl of T7RNA polymerase, and 20 U of RNasin. Also, an experiment in the presence of a membrane system was carried out by adding to this reaction system 2.5 µl of a canine pancreas microsome fraction (Promega). To 3 µl of the resulting reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight

of the translation product was determined by carrying out the autoradiography.

(3) Expression by COS7

5 *Escherichia coli* bearing the expression vector of the protein of the present invention was incubated at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing 100 µg/ml of ampicillin, the helper phage M13KO7 (50 µl) was added, and the incubation was continued at 37°C overnight. A supernatant separated by centrifugation underwent  
10 precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles were suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The culture cells originating from the simian kidney, COS7, were incubated at 37°C in the presence of 5% CO<sub>2</sub> in  
15 the Dulbecco's modified Eagle's culture medium (DMEM) containing 10% fetal calf albumin. Into a 6-well plate (Nunc Inc., 3 cm in the well diameter) were inoculated  $1 \times 10^5$  COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO<sub>2</sub>. After the culture  
20 medium was removed, the cell surface was washed with a phosphate buffer solution and then washed again with DMEM containing 50 mM Tris-hydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM  
25 culture medium, and 3 µl of TRANSFECTAM™ (IBF Inc.) and the resulting mixture was incubated at 37°C for 3 hours in the presence of 5% CO<sub>2</sub>. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf albumin was added,  
30 and the incubation was carried out at 37°C for 2 days in the presence of 5% CO<sub>2</sub>. After the culture medium was replaced by a culture medium containing [<sup>35</sup>S]cystine or

[<sup>35</sup>S]methionine, the incubation was carried out for one hour. After the culture medium and the cells were separated by centrifugation, proteins in the culture fraction and the cell-membrane fraction were subjected to SDS-PAGE.

(4) Clone Examples

<HP00631> (Sequence Nos. 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP00631 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 25-bp 5'-nontranslation region, a 717-bp ORF, and a 343-bp 3'-nontranslation region. The ORF codes for a protein consisting of 238 amino acid residues and there existed five putative transmembrane domains. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in COS7 cells, an expression product of about 25 kDa was observed in the membrane fraction.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the golden hamster androgen-regulated protein FAR-17 (PIR Accession No. A54313). Table 2 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the golden hamster androgen-regulated protein FAR-17 (GH). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 38.0% in the entire

region.

Table 2

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5	HP M-----ALVPCQVLRMAILLSYCSILCNKYKAIEMPSHOTYGGSWKFLTFIDLVIQAVFFG
	* * * * *
	GH MTRTTTCVYHFLVWNWYIFLNY-YIPLIGKDEKLKEFHDGGRSKYLTLLNLLLQAIFFG
	HP ICVLTDLSSLLTRGSGNQEQERQLKKLI-SLRDWMLAVLAFVGVFVAVFWIYAYDRE
	* * * * *
10	GH VACLDD---VLKRIIG-----RKDIKFITSTRDLLFSTLVFPFISTFIFLVFWTLFYDRS
	HP MIYPKLLDNFIPGWLNHGMHTTVLPFILEMRTSHHQYPSRSSGLTAICTFSVGYILWVC
	*****
	GH LIYPKGLDDYFPAWLNHAMHTYILLFVLVETILRPHHYPSKKLGLALLGACNLAYITRVL
	HP WVHVHTGMWVYPFLEHIGPGARIIFFGSTILMNFLLYLLGEVLNNYIW-DTQKSMEEEKE
15	* * * * *
	GH WRYSQTGNWVYPVFASLNPLGIIFFFLVCYILNASIYLVGEKINHVKWGATVK---PLMK
	HP KPKLE
	* *
	GH KKK---

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R22829) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02403> (Sequence Nos. 2, 12, and 23)

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Determination of the whole base sequence of the cDNA insert of clone HP02403 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 6-bp 5'-nontranslation region, a 585-bp ORF, and a 577-

bp 3'-nontranslation region. The ORF codes for a protein consisting of 194 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost identical with the molecular weight of 21,959 predicted from the ORF. When expressed in COS7 cells, an expression product of about 21 kDa was observed in the membrane fraction.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the Japanese quail apoptosis regulator NR-13 (SWISS-PROT Accession No. Q90343). Table 3 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the Japanese quail apoptosis regulator NR-13 (CC). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 31.5% in the entire region.

Table 3

HP MADPLRERTELLLADYLYGCAREPGTPEPAPSTPEAAVLRSAARLRQIHRSFF--SAYL  
\* \* \* \* \*  
5 CC MPGSLKEETALLLEDYFQHRA---GGAALPPS-ATAAELRRAAAELERRERPFFRSCAPL  
HP GYPGNRFELVAL--MADSVLSDSPGPTWGRVVTLVTFA GTLLERG PLVTARWKKGWFQPR  
\* \* \* \* \*  
CC ARAEPR-EAAA LLRKVAAQLET DGGLNWGRLLALVVFAGTL-----A  
HP LKEQEGDVARD CQRLVALLSSRLMGQHRAWLQA QGGWDGFCHFF-RTPFPLAFWRKQLVQ  
10 \* \* \* \* \*  
CC AALAESACEEGPSRLAAALTAYLAEEQGEWMEEHGGWDGFCRFFGRHG SQPADQNSTLSN  
HP A-FLSCLLTAFIYLWTRLL  
\* \*  
CC AIMAAAGFGIAGLAFLLVVR

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA098865) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

**<HP02420> (Sequence Nos. 3, 13, and 25)**

25 Determination of the whole base sequence of the cDNA  
insert of clone HP02420 obtained from cDNA libraries of human  
stomach cancer revealed the structure consisting of a 35-bp 5'-  
nontranslation region, a 420-bp ORF, and a 169-bp 3'-  
nontranslation region. The ORF codes for a protein consisting  
30 of 139 amino acid residues and there existed three putative  
transmembrane domains. Figure 3 depicts the  
hydrophobicity/hydrophilicity profile, obtained by the Kyte-

Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 17 kDa that was almost identical with the molecular weight of 16,082 predicted from the ORF. When expressed in C07 cells, an expression product of about 16 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of sequences that were analogous to a yeast hypothetical protein of 15.9 kDa (SWISS-PROT Accession No. P53173). Table 4 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the yeast hypothetical protein of 15.9 kDa (SC). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 43.2% in the entire region.

20

Table 4

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	HP	MEAVVFVFSLLDCCALIFLSVYFIITLSDLCDYINARSCCSKLNKWWIPELIGHTIVTV
		*.* .*. . . . . * .* *.*.* .*** .***. . .***.* .*** *
	SC	MGAWLFILAVVNCINLFGQVHFTILYADLEADYINPIELCSKVNKLTPEAALHGALS
25	HP	LLIMSLHWFIPLLNPVATWNIYRYIMVPSGNMGVDFPTEIHNRGQLKSHMKEAMIKLGF
		*.*.. .**.* . . . . . * . . . . .***.* * .* .***.* .***
	SC	LFLNNGYWFVFLNLPVLA---YNLNKI-YNKVQLDATEIF-RT-LGKHKRESFLKLGF
	HP	HLLCFFMYLYSMILALIND
		*** **.* .***.* .***.* .
30	SC	HLLMFFFYLYRMIMALIAESGDDF

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA044799) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10349> (Sequence Nos. 4, 14, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP10349 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 16-bp 5'-nontranslation region, a 972-bp ORF, and a 133-bp 3'-nontranslation region. The ORF codes for a protein consisting of 323 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 36 kDa that was almost identical with the molecular weight of 36,200 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. F13066) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10508> (Sequence Nos. 5, 15, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10508 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of

a 33-bp 5'-nontranslation region, a 696-bp ORF, and a 98-bp 3'-nontranslation region. The ORF codes for a protein consisting of 231 amino acid residues and there existed four transmembrane domains. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in C07 cells, an expression product of about 22 kDa was observed in the supernatant fraction and the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA484181) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10524> (Sequence Nos. 6, 16, and 31)

Determination of the whole base sequence of the cDNA insert of clone HP10524 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 308-bp 5'-nontranslation region, a 294-bp ORF, and a 587-bp 3'-nontranslation region. The ORF codes for a protein consisting of 97 amino acid residues and possessed one transmembrane domain. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 21 kDa that was larger than the molecular weight of 10,673 predicted from the ORF. When expressed in COS cells, an expression product of about 26 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the human glycoporphin C (SWISS-PROT Accession No. P04921). Table 5 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the human glycoporphin C (GP). Therein, the marks of - and \* represent a gap and an amino acid residue identical with the protein of the present invention, respectively. The both proteins possessed a homology of 30.5% in the entire region.

Table 5

15	HP M-----TSLLTTP---SPREELMTTPILQPTTEALS-PEDG---AST-----A
	*                **   *   *                ** *   *   *   **   **
	GP MWSTRSPNSTAWPLSLEPDPGMASASTTMHTTTIAEPDPGMSGWPDGRMETSTPTIMDIV
	HP LIAVVITVVFLTLLSVVILIFFYLYKNKGSYVTYE--PTEGEPSAIVQMESD----LAKG
	***   *   *                *   *   ** *   *   *   **   **                *   *
	GP VIAGVIAAIVLVSLLFVMLRMYRHKGTYHTNEAKGTEFAESADAALQGDPAQDAGD
20	HP SEKEEYFI
	*        *****
	GP SSRKEYFI

25 Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R21992) in EST, but, since they are partial sequences, it can not be judged

30 whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10529> (Sequence Nos. 7, 17, and 33)

Determination of the whole base sequence of the cDNA insert of clone HP10529 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 93-bp 5'-nontranslation region, a 597-bp ORF, and an 810-bp 3'-nontranslation region. The ORF codes for a protein consisting of 198 amino acid residues and possessed two transmembrane domains. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the fugu rubripes putative protein 2 (GenBank Accession No. AF026198). Table 6 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the fugu rubripes putative protein 2 (FR). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 56.1% in the entire region.

Table 6

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obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight. When expressed in COS cells, an expression product of about 14 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. R36207) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10549> (Sequence Nos. 9, 19, and 37)

Determination of the whole base sequence of the cDNA insert of clone HP10549 obtained from cDNA libraries of the human stomach cancer revealed the structure consisting of an 11-bp 5'-nontranslation region, a 606-bp ORF, and a 1101-bp 3'-nontranslation region. The ORF codes for a protein consisting of 201 amino acid residues and possessed three putative transmembrane domains. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was larger than the molecular weight of 23,346 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. N28687) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10551> (Sequence Nos. 10, 20, and 39)

Determination of the whole base sequence of the cDNA insert of clone HP10551 obtained from cDNA libraries of the human stomach cancer revealed the structure consisting of a 152-bp 5'-nontranslation region, a 750-bp ORF, and a 93-bp 3'-nontranslation region. The ORF codes for a protein consisting of 249 amino acid residues and possessed four putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the nematode imaginary protein T15B7 (GenBank Accession No. F022985). Table 7 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the nematode imaginary protein T15B7 (CE). Therein, the marks of -, \*, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 41.3% in the entire region.

Table 7

20 Furthermore, the search of the GenBank using the base  
sequences of the present cDNA has revealed the  
registration of sequences that possessed a homology of 90%  
or more (for example, Accession No. N67509) in EST, but,  
since they are partial sequences, it can not be judged  
25 whether or not any of these sequences codes for the same  
protein as the protein of the present invention.

## INDUSTRIAL APPLICABILITY

30       The present invention provides human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors of these DNAs as well as eucaryotic cells expressing these DNAs. All of the proteins of the present invention are secreted or exist in the cell

membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as  
5 carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the  
10 gene therapy. Furthermore, the DNAs can be utilized for large-scale expression of these proteins. Cells, wherein these genes are introduced to express these proteins, can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular  
15 pharmaceuticals, and so on.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from  
20 which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively  
25 spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the  
30 disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is

a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified  
5 expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene  
10 (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of  
15 the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic  
20 control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s)  
25 corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene  
30 inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal

et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably  
5 detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with  
10 altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of  
15 molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular  
20 and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such  
25 domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a  
30 disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein,

where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions,

more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) <sup>†</sup>	Hybridization Temperature and Buffer <sup>†</sup>	Wash Temperature and Buffer <sup>†</sup>
A	DNA : DNA	≥50	65°C; 1×SSC -or- 42°C; 1×SSC, 50% formamide	65°C; 0.3×SSC
B	DNA : DNA	<50	T <sub>B</sub> *; 1×SSC	T <sub>B</sub> *; 1×SSC
C	DNA : RNA	≥50	67°C; 1×SSC -or- 45°C; 1×SSC, 50% formamide	67°C; 0.3×SSC
D	DNA : RNA	<50	T <sub>D</sub> *; 1×SSC	T <sub>D</sub> *; 1×SSC
E	RNA : RNA	≥50	70°C; 1×SSC -or- 50°C; 1×SSC, 50% formamide	70°C; 0.3×SSC
F	RNA : RNA	<50	T <sub>F</sub> *; 1×SSC	T <sub>F</sub> *; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or- 42°C; 4×SSC, 50% formamide	65°C; 1×SSC
H	DNA : DNA	<50	T <sub>H</sub> *; 4×SSC	T <sub>H</sub> *; 4×SSC
I	DNA : RNA	≥50	67°C; 4×SSC -or- 45°C; 4×SSC, 50% formamide	67°C; 1×SSC
J	DNA : RNA	<50	T <sub>J</sub> *; 4×SSC	T <sub>J</sub> *; 4×SSC
K	RNA : RNA	≥50	70°C; 4×SSC -or- 50°C; 4×SSC, 50% formamide	67°C; 1×SSC
L	RNA : RNA	<50	T <sub>L</sub> *; 2×SSC	T <sub>L</sub> *; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or- 40°C; 6×SSC, 50% formamide	50°C; 2×SSC
N	DNA : DNA	<50	T <sub>N</sub> *; 6×SSC	T <sub>N</sub> *; 6×SSC
O	DNA : RNA	≥50	55°C; 4×SSC -or- 42°C; 6×SSC, 50% formamide	55°C; 2×SSC
P	DNA : RNA	<50	T <sub>P</sub> *; 6×SSC	T <sub>P</sub> *; 6×SSC
Q	RNA : RNA	≥50	60°C; 4×SSC -or- 45°C; 6×SSC, 50% formamide	60°C; 2×SSC
R	RNA : RNA	<50	T <sub>R</sub> *; 4×SSC	T <sub>R</sub> *; 4×SSC

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH<sub>2</sub>PO<sub>4</sub>, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

\*T<sub>B</sub> - T<sub>R</sub> : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T<sub>m</sub>) of the hybrid, where T<sub>m</sub> is determined according to the following equations. For hybrids less than 18 base pairs in length, T<sub>m</sub>(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T<sub>m</sub>(°C)=81.5 + 16.6(log<sub>10</sub>[Na<sup>+</sup>]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na<sup>+</sup>] is the concentration of sodium ions in the hybridization buffer ([Na<sup>+</sup>] for 1×SSC=0.165M).

20

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the

hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

## CLAIMS

1. A protein comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10.

5        2. A DNA coding for the protein according to Claim 1.

3. A cDNA comprising any of the base sequences represented by Sequence Nos. 11 to 20.

10       4. The cDNA according to Claim 3 comprising any of the base sequences represented by Sequence Nos. 21, 23, 25, 27, 29, 31, 33, 35, 37 and 39.

5. An expression vector capable of expressing the DNA according to any of Claims 2 to 4 by in vitro translation or in eucaryotic cells.

15       6. A transformation eucaryotic cell capable of expressing the DNA according to any of Claims 2 to 4 to produce the protein according to Claim 1.

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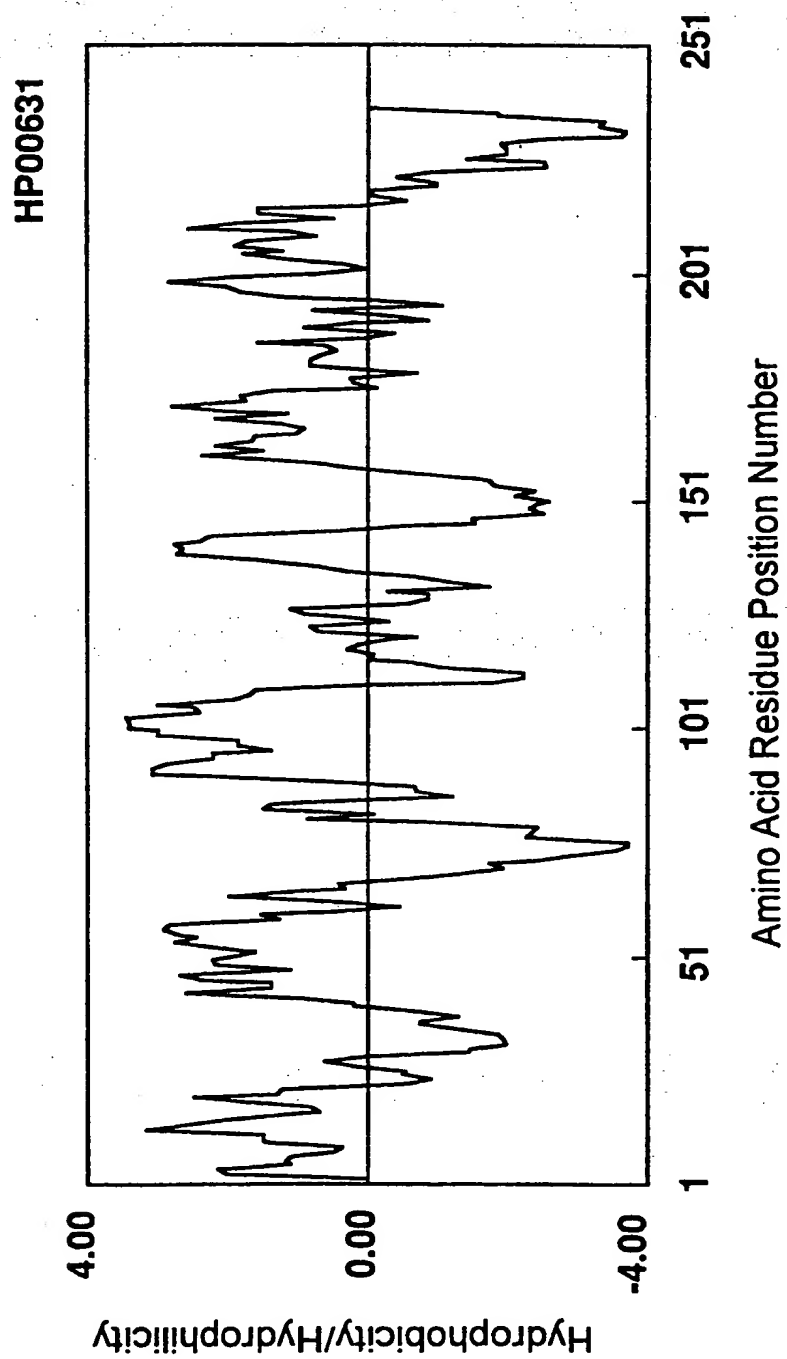


Fig. 1

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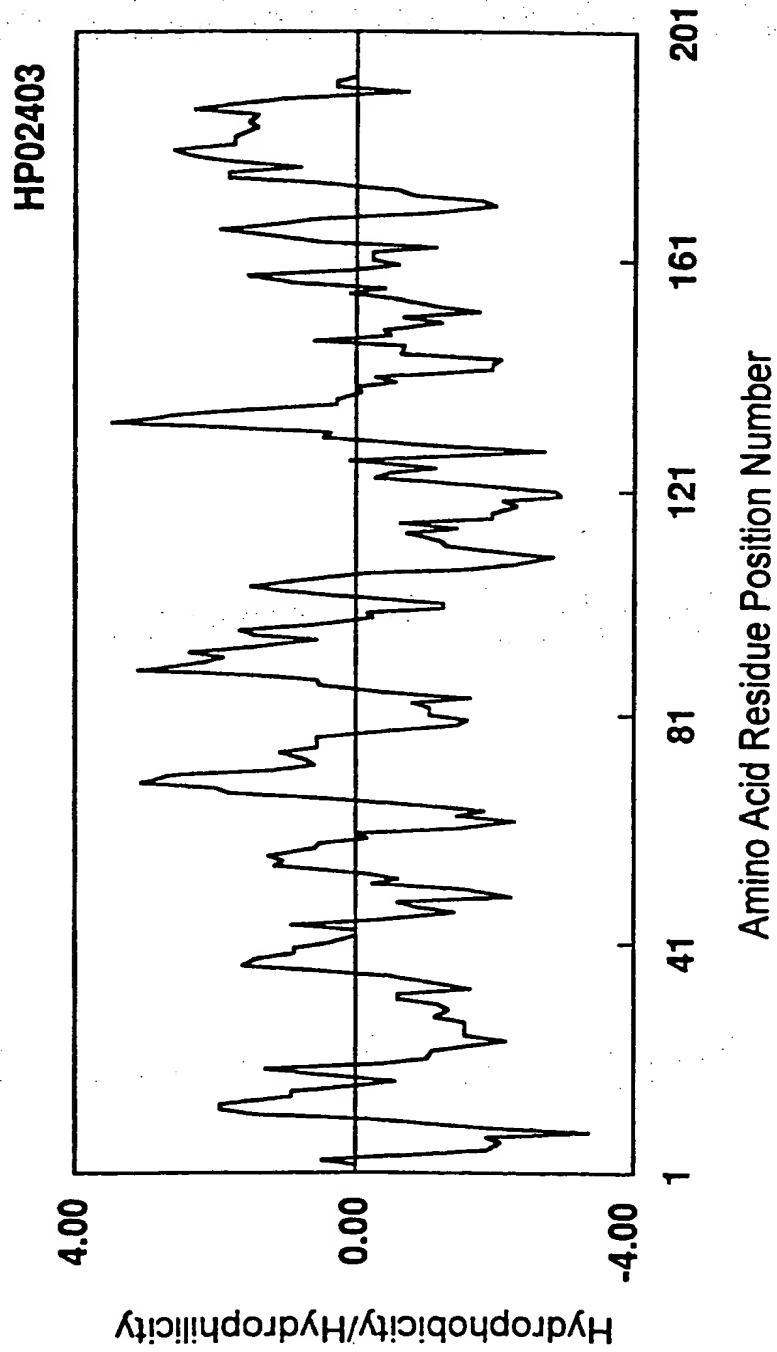


Fig. 2

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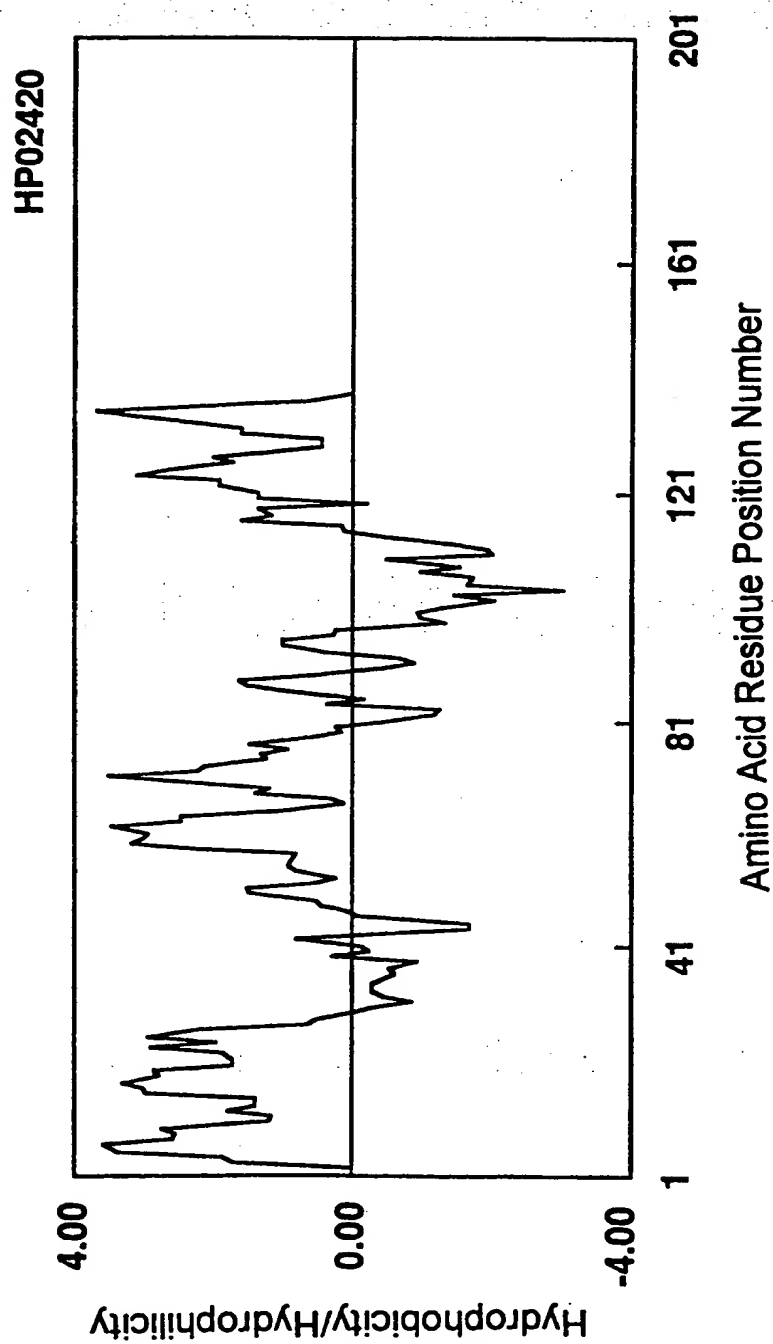


Fig. 3

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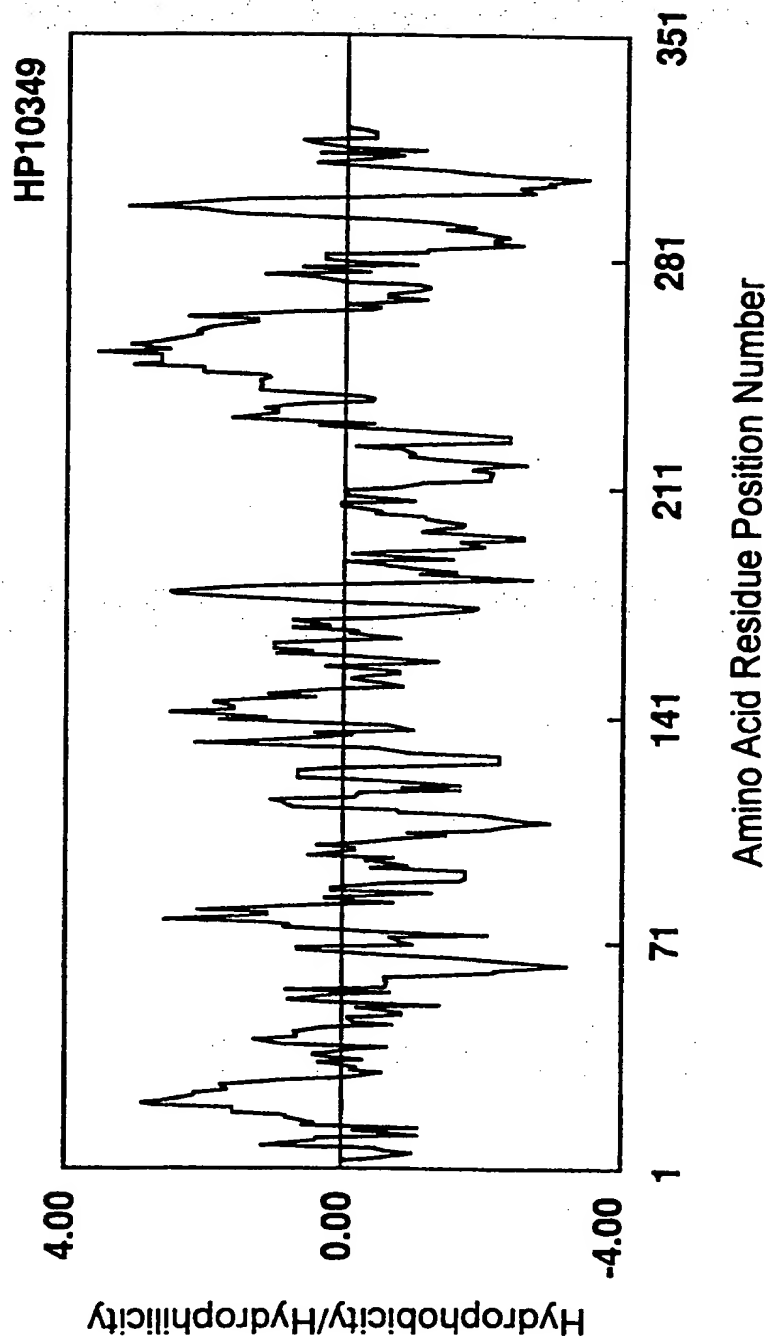


Fig. 4

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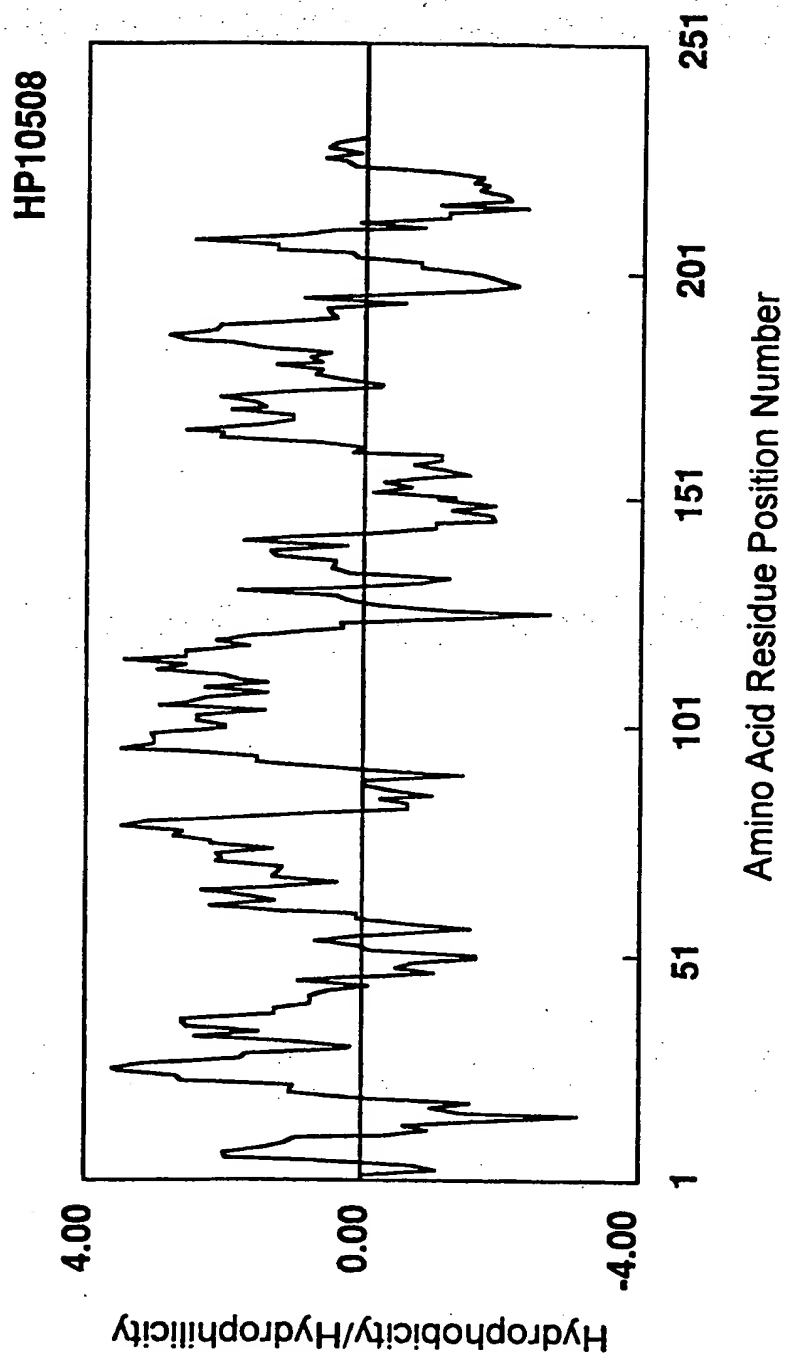


Fig. 5

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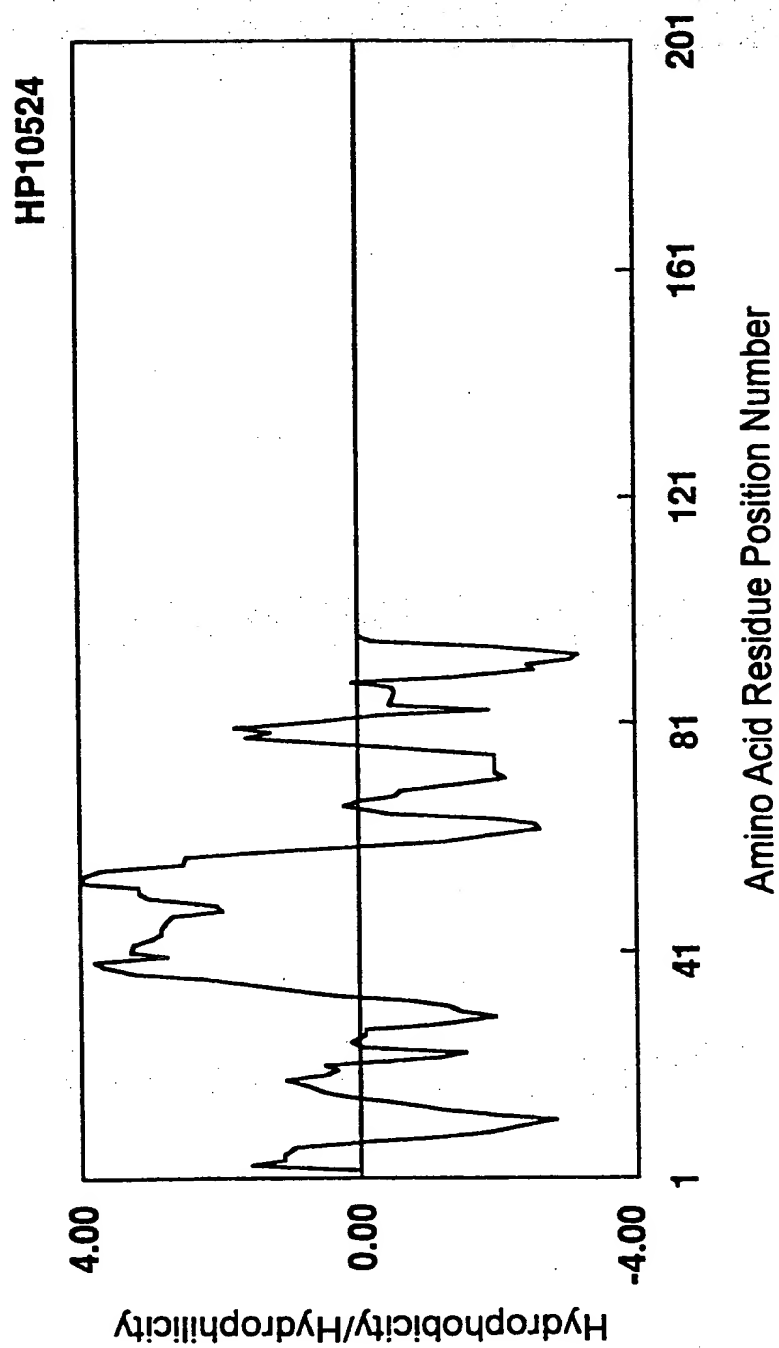


Fig. 6

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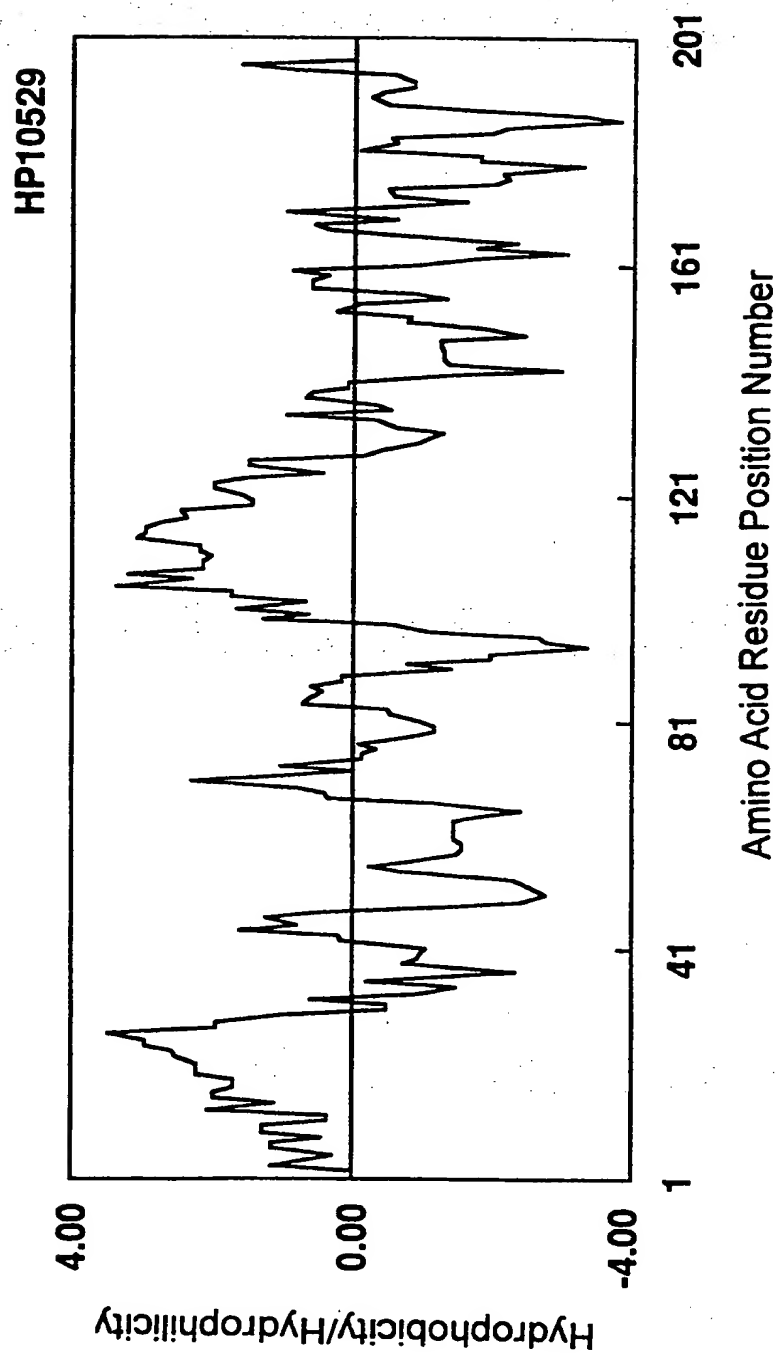


Fig. 7

8/10

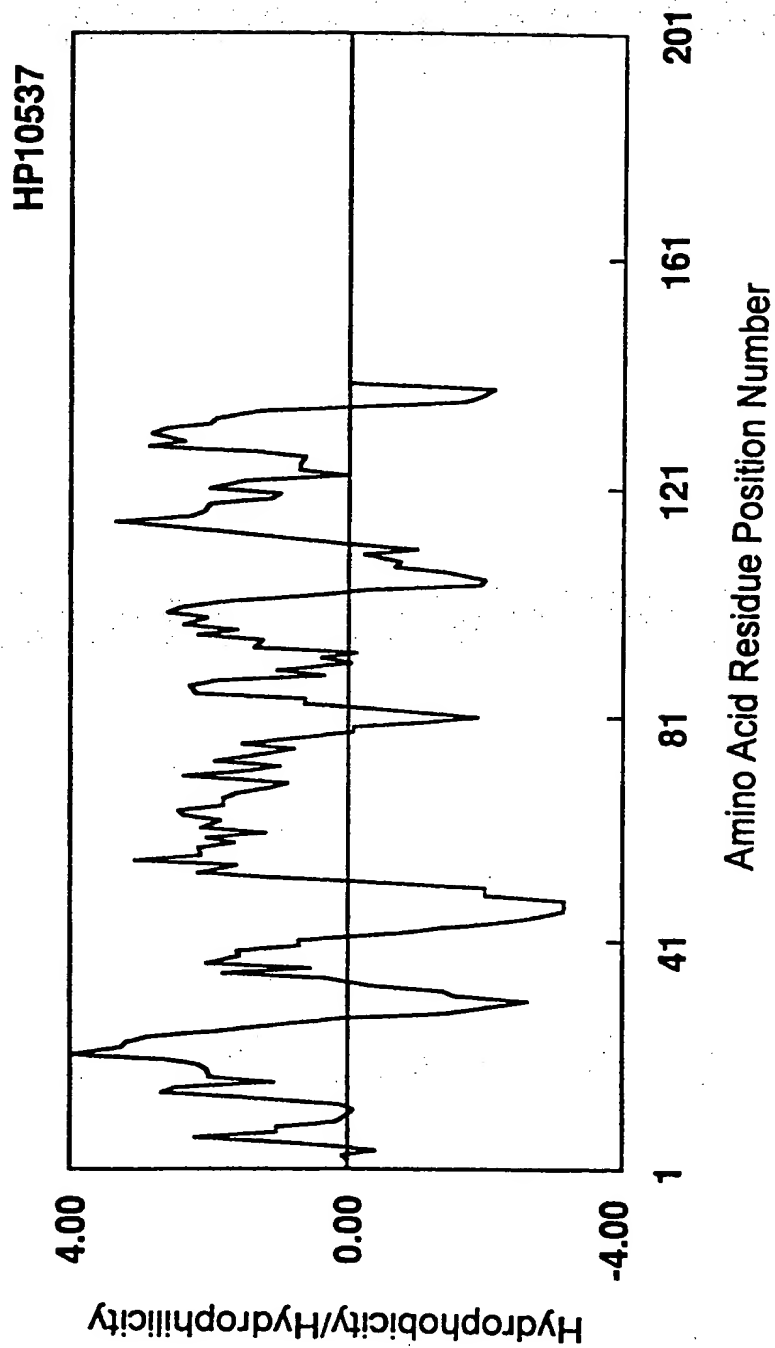


Fig. 8

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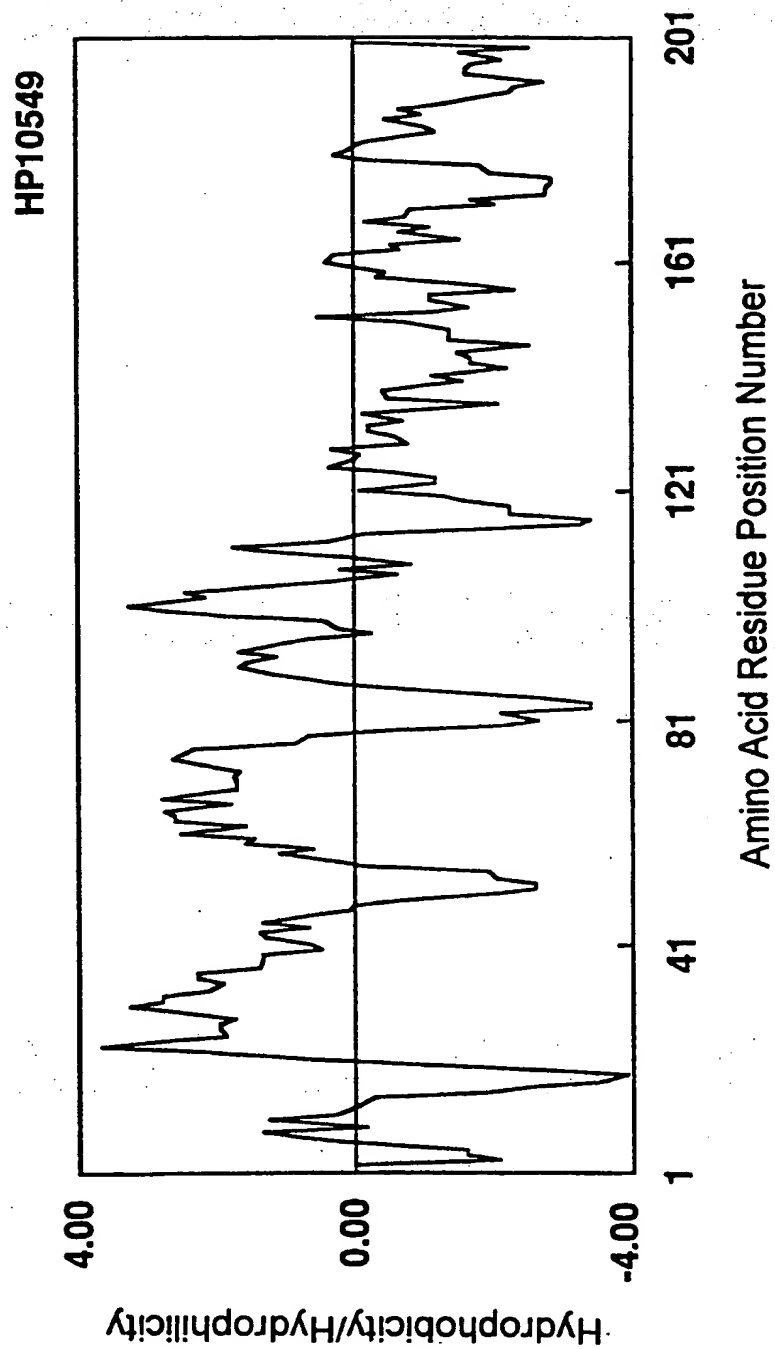


Fig. 9

10/10

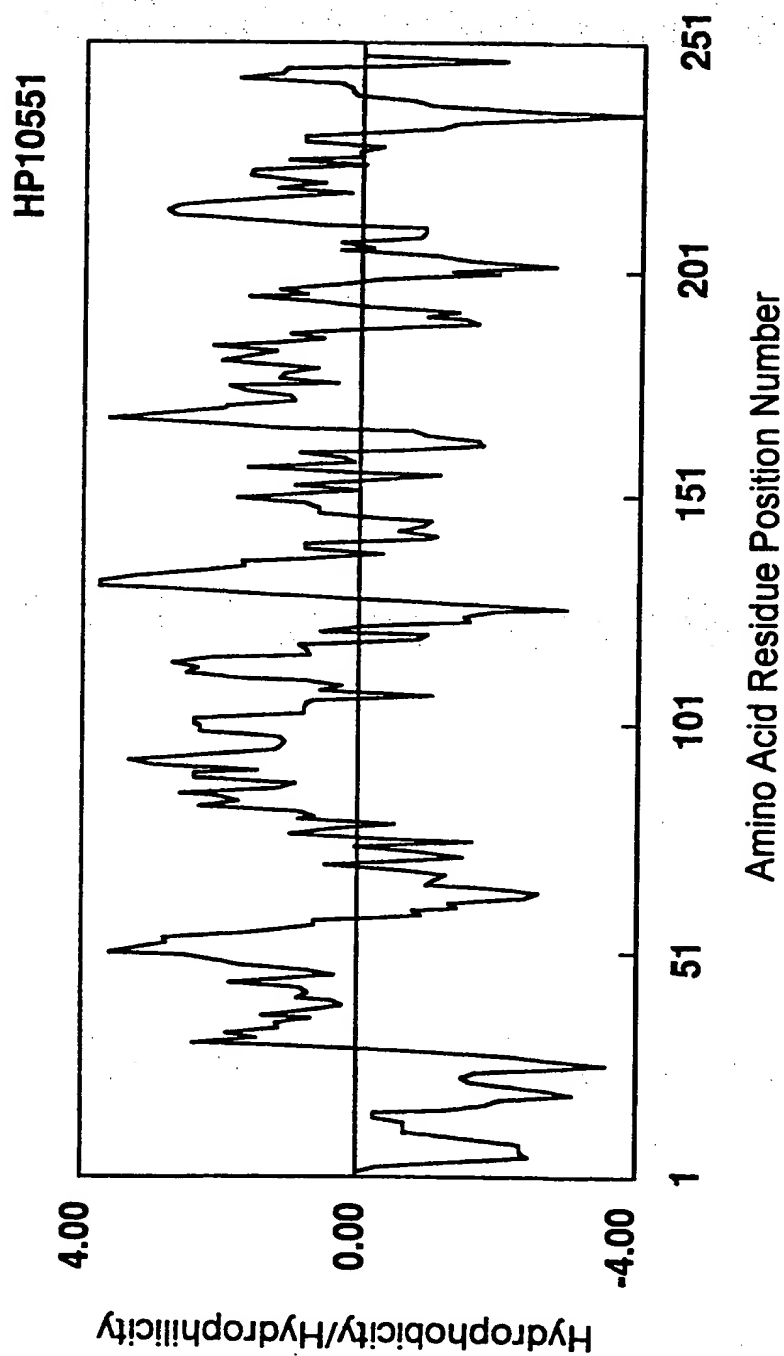


Fig. 10

**Sequence listing**

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<150> JP 10-180008

<151> 1998-06-26

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Gln Thr Tyr Gly Gly Ser Trp Lys Phe Leu Thr Phe Ile Asp Leu Val

30 35 40 45

Ile Gln Ala Val Phe Phe Gly Ile Cys Val Leu Thr Asp Leu Ser Ser

50 55 60

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Leu Leu Thr Arg Gly Ser Gly Asn Gln Glu Gln Glu Arg Gln Leu Lys  
 65 70 75 80  
 Lys Leu Ile Ser Leu Arg Asp Trp Met Leu Ala Val Leu Ala Phe Pro  
 85 90 95  
 5 Val Gly Val Phe Val Val Ala Val Phe Trp Ile Ile Tyr Ala Tyr Asp  
 100 105 110  
 Arg Glu Met Ile Tyr Pro Lys Leu Leu Asp Asn Phe Ile Pro Gly Trp  
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 Leu Asn His Gly Met His Thr Thr Val Leu Pro Phe Ile Leu Ile Glu  
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 Met Arg Thr Ser His His Gln Tyr Pro Ser Arg Ser Ser Gly Leu Thr  
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 Ala Ile Cys Thr Phe Ser Val Gly Tyr Ile Leu Trp Val Cys Trp Val  
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 15 His His Val Thr Gly Met Trp Val Tyr Pro Phe Leu Glu His Ile Gly  
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 Pro Gly Ala Arg Ile Ile Phe Phe Gly Ser Thr Thr Ile Leu Met Asn  
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 Ile His Arg Ser Phe Phe Ser Ala Tyr Leu Gly Tyr Pro Gly Asn Arg  
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 Phe Glu Leu Val Ala Leu Met Ala Asp Ser Val Leu Ser Asp Ser Pro  
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 Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala Gly Thr  
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 Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg Asp Cys  
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 20 Phe Leu Ser Cys Leu Leu Thr Thr Ala Phe Ile Tyr Leu Trp Thr Arg  
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 Leu Leu

&lt;210&gt; 3

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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 3

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10

15

Ile Phe Leu Ser Val Tyr Phe Ile Ile Thr Leu Ser Asp Leu Glu Cys

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 Ser Leu His Trp Phe Ile Phe Leu Leu Asn Leu Pro Val Ala Thr Trp  
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 Asn Ile Tyr Arg Tyr Ile Met Val Pro Ser Gly Asn Met Gly Val Phe  
 85 90 95  
 10 Asp Pro Thr Glu Ile His Asn Arg Gly Gln Leu Lys Ser His Met Lys  
 100 105 110  
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 35 40 45  
 His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr Tyr Pro Lys Glu  
 30 50 55 60  
 Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu Phe Ser Ile Cys  
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5/45

Gln Phe Val Asp Asp Gly Ile Asp Leu Asn Arg Thr Lys Leu Glu Cys  
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 Glu Gln Leu Met Ser Leu Met Pro Lys Met His Leu Leu Phe Pro Leu  
                     130                    135                    140  
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 Phe Ile Thr Ser Ser Trp Thr Phe Tyr Leu Gln Ala Asp Asp Gly Lys  
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 Ile Val Ile Phe Gln Ser Lys Pro Glu Ile Gln Tyr Ala Pro His Leu  
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                     195                    200                    205  
 Tyr Leu Gln Met Arg Asn Ser Gln Ala His Arg Asn Phe Leu Glu Asp  
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 Gly Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu Asn Ser Gly Trp  
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 Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val Leu Leu Trp Ile  
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 Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr Val Pro Ser Glu  
                     260                    265                    270  
 25 Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn Glu Gln Lys Leu  
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 Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg Ser Lys Thr Glu  
                     290                    295                    300  
 Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys Val Asn Leu Ala His  
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 Ser Glu Ile

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&lt;210&gt; 5

&lt;211&gt; 231

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

5

&lt;400&gt; 5

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Arg Leu Met Arg Val Gly Leu Ala Leu Ile Leu Val Gly His Val Asn

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Leu Leu Leu Gly Ala Val Leu His Gly Thr Val Leu Arg His Val Ala

35 40 45

Asn Pro Arg Gly Ala Val Thr Pro Glu Tyr Thr Val Ala Asn Val Ile

50 55 60

15 Ser Val Gly Ser Gly Leu Leu Ser Val Ser Val Gly Leu Val Ala Leu

65 70 75 80

Leu Ala Ser Arg Asn Leu Leu Arg Pro Pro Leu His Trp Val Leu Leu

85 90 95

Ala Leu Ala Leu Val Asn Leu Leu Leu Ser Val Ala Cys Ser Leu Gly

20 100 105 110

Leu Leu Leu Ala Val Ser Leu Thr Val Ala Asn Gly Gly Arg Arg Leu

115 120 125

Ile Ala Asp Cys His Pro Gly Leu Leu Asp Pro Leu Val Pro Leu Asp

130 135 140

25 Glu Gly Pro Gly His Thr Asp Cys Pro Phe Asp Pro Thr Arg Ile Tyr

145 150 155 160

Asp Thr Ala Leu Ala Leu Trp Ile Pro Ser Leu Leu Met Ser Ala Gly

165 170 175

Glu Ala Ala Leu Ser Gly Tyr Cys Cys Val Ala Ala Leu Thr Leu Arg

30 180 185 190

Gly Val Gly Pro Cys Arg Lys Asp Gly Leu Gln Gly Gln Val Val Ala

195 200 205

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Gly Cys Asp Ala Arg Val Lys Gln Lys Ala Trp Gln Pro Arg Phe Pro

210

215

220

Gly Ile Lys Val Lys Ala Leu

225

230

5

&lt;210&gt; 6

&lt;211&gt; 97

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

10

&lt;400&gt; 6

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1

5

10

15

Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp Gly Ala

15

20

25

30

Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu Thr Leu

35

40

45

Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn Lys Gly

50

55

60

20

Ser Tyr Val Thr Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala Ile Val

65

70

75

80

Gln Met Glu Ser Asp Leu Ala Lys Gly Ser Glu Lys Glu Glu Tyr Phe

85

90

95

Ile

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&lt;210&gt; 7

&lt;211&gt; 198

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

30

&lt;400&gt; 7

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8/45

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		50		55		60										
	Asp	Cys	Asp	Cys	Leu	His	Val	Val	Glu	Pro	Met	Pro	Val	Arg	Gly	Pro
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		85		90		95										
	Ser	Ser	Val	Thr	Ile	Lys	Val	Thr	Ile	Ile	Ile	Tyr	Leu	Ser	Ile	Leu
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	Gly	Leu	Leu	Leu	Leu	Tyr	Met	Val	Tyr	Leu	Thr	Leu	Val	Glu	Pro	Ile
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		165		170		175										
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&lt;211&gt; 140

&lt;212&gt; PRT

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&lt;400&gt; 8

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 Ala Val Glu Leu Ala Gly Phe Leu Ser Gly Val Ser Met Phe Asn Ser  
 10 65 70 75 80  
 Thr Gln Ser Leu Ile Ser Ile Gly Ala His Cys Ser Ala Ser Val Ala  
 85 90 95  
 Leu Ser Phe Phe Ile Phe Glu Arg Trp Glu Cys Thr Thr Tyr Trp Tyr  
 100 105 110  
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 35 40 45  
 Gly Trp Lys Arg His Gly Ala His Ile Tyr Leu Thr Met Leu Leu Ser

10/45

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 Ile Ala Ile Trp Val Ala Trp Ile Thr Leu Leu Met Leu Pro Asp Phe  
 65 70 75 80  
 Asp Arg Arg Trp Asp Asp Thr Ile Leu Ser Ser Ala Leu Ala Ala Asn  
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 Gly Trp Val Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe Trp Leu Leu  
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 Thr Lys Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp Ala Phe Cys  
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 10 Lys Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn Arg Ala Tyr  
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 Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly Asp Thr Leu  
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 Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln Pro Pro Gln  
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 His Arg Gly Leu Tyr Lys Ser Ile Gln Lys Thr Leu Lys Phe Phe Gln  
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 5 Thr Phe Ala Leu Leu Glu Ile Val His Cys Leu Ile Gly Ile Val Pro  
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 Thr Ser Val Ile Val Thr Gly Val Gln Val Ser Ser Arg Ile Phe Met  
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 Val Trp Leu Ile Thr His Ser Ile Lys Pro Ile Gln Asn Glu Glu Ser  
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 Ser Phe Tyr Thr Phe Ser Leu Leu Asp His Leu Pro Tyr Phe Ile Lys  
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 15 Trp Ala Arg Tyr Asn Phe Phe Ile Ile Leu Tyr Pro Val Gly Val Ala  
 165 170 175  
 Gly Glu Leu Leu Thr Ile Tyr Ala Ala Leu Pro His Val Lys Lys Thr  
 180 185 190  
 Gly Met Phe Ser Ile Arg Leu Pro Asn Lys Tyr Asn Val Ser Phe Asp  
 20 195 200 205  
 Tyr Tyr Tyr Phe Leu Leu Ile Thr Met Ala Ser Tyr Ile Pro Leu Phe  
 210 215 220  
 Pro Gln Leu Tyr Phe His Met Leu Arg Gln Arg Arg Lys Val Leu His  
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&lt;213&gt; Homo sapiens

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&lt;211&gt; 582

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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13/45

&lt;211&gt; 417

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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 cagtttgtgg atgatggaat tgacttaaata cgaactaaat tggaatgtga atctgcatgt 300  
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14/45

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15/45

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 aagaacaaaag gcagctacgt cacctatgaa cctacagaag gtgagcccag tgccatcgtc 240  
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 agatgtaaat gtatctgccc tccctataaa gaaaattctg ggcatattta taataagaac 180  
 atatctcaga aagattgtga ttgccttcat gttgtggagc ccatgcctgt gcgggggcct 240  
 15 gatgtagaag catactgtct acgctgtgaa tgcaaataat aagaaagaag ctctgtcaca 300  
 atcaaggtta ccattataat ttatctctcc attttgggcc ttctacttct gtacatggta 360  
 tatcttactc tggttgagcc catactgaag aggcgcctct ttggacatgc acagttgata 420  
 cagagtgatg atgatattgg ggatcaccag ccttttgcaa atgcacacga tgtgctagcc 480  
 cgctcccgca gtcgagccaa cgtgctgaac aaggtagaat atgcacagca gcgctggaag 540  
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 <212> DNA

25 <213> Homo sapiens

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 30 ttcacccccg aggagtatga caagcaggac attcagctgg tggccgcgct ctctgtcacc 180  
 ctgggcctct ttgcagtgga gctggccggt ttctctcag gagtctccat gttcaacagc 240  
 acccagagcc tcactctccat tggggctcac tgtagtgcac ccgtggccct gtccttcttc 300

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atattcgagc gttgggagtg cactacgtat tggtagattt ttgtcttctg cagtgcctt 360  
ccagctgtca ctgaaatggc ttattctgtc accgtctttg ggctgaaaaa gaaacccttc 420

&lt;210&gt; 19

5 &lt;211&gt; 603

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 19

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ttcactttct gtgggttctt cacgggctgg aagagacatg gggccacat ctacctcacg 180  
atgtctctct ccattgccat ctgggtggcc tggatcacc tgctcatgct tcttgacttt 240  
gaccgcaggt gggatgacac catctcagc tccgccttgg ctgccaatgg ctgggtgttc 300  
15 ctggttggtt atgttagtcc cgagttttgg ctgctcaca agcaacgaaa ccccatggat 360  
tactctgttg aggatgcttt ctgtaaacct caactcgtga agaagagcta tgggtgtggag 420  
aacagagcct actctcaaga ggaaatcact caaggttttg aagagacagg ggacacgctc 480  
tatgccccct attccacaca ttttcagctg cagaaccagc ctccccaaaa ggaattctcc 540  
atcccacggg cccacgcttg gccgagccct taaaaagact atgaagtaaa gaaagagggc 600  
20 agc 603

&lt;210&gt; 20

&lt;211&gt; 747

&lt;212&gt; DNA

25 &lt;213&gt; Homo sapiens

&lt;400&gt; 20

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gaggctcccg gcaagcggag ggcctgggg ttcttgcca ccgcctggct caccttctac 120  
30 gacatgccca tgaccgcggg gtgggtggtt ctagtattg ccatggtacg tttttatatg 180  
gaaaaaggaa cacacagagg tttatataaa agtattcaga agacacttaa atttttccag 240  
acatttgctt tgcttgagat agttcactgt ttaattggaa ttgtacctac ttctgtgatt 300

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	gtgactgggg tccaagtgag ttcaagaatc tttatgggtg ggctcattac tcacagtata	360
	aaaccaatcc agaatgaaga gagtgtggtg ctttttctgg tcgcgtggac tgtgacagag	420
	atcactcgct attccttota cacattcagc cttcttgacc acttgccata cttcattaaa	480
	tgggocagat ataatttttt tatcatotta tatcctgttg gagttgctgg tgaacttctt	540
5	acaatatacg ctgccttgcc gcatgtgaag aaaacaggaa tgttttcaat aagacttcct	600
	aacaaataca atgtctcttt tgactactat tattttcttc ttataaccat ggcacatat	660
	atacctttgt ttocacaact ctattttcat atgttacgtc aaagaagaaa ggtgcttcat	720
	ggagaggtga ttgtagaaaa ggatgat	747
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	Met Ala Leu Val Pro Cys Gln Val Leu	
	1 5	
	cgg atg gca atc ctg ctg tct tac tgc tct atc ctg tgt aac tac aag	100
20	Arg Met Ala Ile Leu Leu Ser Tyr Cys Ser Ile Leu Cys Asn Tyr Lys	
	10 15 20 25	
	gcc atc gaa atg ccc tca cac cag acc tac gga ggg agc tgg aaa ttc	148
	Ala Ile Glu Met Pro Ser His Gln Thr Tyr Gly Gly Ser Trp Lys Phe	
	30 35 40	
25	ctg acg ttc att gat ctg gtt atc cag gct gtc ttt ttt ggc atc tgt	196
	Leu Thr Phe Ile Asp Leu Val Ile Gln Ala Val Phe Phe Gly Ile Cys	
	45 50 55	
	gtg ctg act gat ctt tcc agt ctt ctg act cga gga agt ggg aac cag	244
	Val Leu Thr Asp Leu Ser Ser Leu Leu Thr Arg Gly Ser Gly Asn Gln	
30	60 65 70	
	gag caa gag agg cag ctc aag aag ctc atc tct ctc cgg gac tgg atg	292
	Glu Gln Glu Arg Gln Leu Lys Lys Leu Il Ser Leu Arg Asp Trp Met	

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	75	80	85	
	tta gct gtg ttg gcc ttt cct gtt ggg gtt ttt gtt gta gca gtg ttc			340
	Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val Phe			
	90	95	100	105
5	tgg atc att tat gcc tat gac aga gag atg ata tac ccg aag ctg ctg			388
	Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu Leu			
	110	115	120	
	gat aat ttt atc cca ggg tgg ctg aat cac gga atg cac acg acg gtt			436
	Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr Val			
10	125	130	135	
	ctg ccc ttt ata tta atc gag atg agg aca tcg cac cat cag tat ccc			484
	Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr Pro			
	140	145	150	
	agc agg agc agc gga ctt acc gcc ata tgt acc ttc tct gtt ggc tat			532
15	Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly Tyr			
	155	160	165	
	ata tta tgg gtg tgc tgg gtg cat cat gta act ggc atg tgg gtg tac			580
	Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val Tyr			
	170	175	180	185
20	cct ttc ctg gaa cac att ggc cca gga gcc aga atc atc ttc ttt ggg			628
	Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe Gly			
	190	195	200	
	tct aca acc atc tta atg aac ttc ctg tac ctg ctg gga gaa gtt ctg			676
	Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val Leu			
25	205	210	215	
	aac aac tat atc tgg gat aca cag aaa agt atg gaa gaa gag aaa gaa			724
	Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys Glu			
	220	225	230	
	aag cct aaa ttg gaa tgagatccaa gtctaaacgc aagagctaga ttgagccgcc a			780
30	Lys Pro Lys Leu Glu			
	235			
	ttgaagactc cttccctcg ggcattggca gtgggggaga aaaggcttca aaggaacttg			840

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gtggcatcag cacccccctc ccccaatgag gacacctttt atatataaat atgtataaac 900  
 atagaataca gttgtttcca aaagaactca cctcactgt gtgttaaaga attcttccca 960  
 aagtcattac tgataataac atttttttcc ttttctagtt ttaaaaccag aattggacct 1020  
 tggattttta ttttggcaat tgtaactcca tctaatacaag aaagaataaa agttttattgc 1080  
 5 acttc 1085

&lt;210&gt; 22

&lt;211&gt; 238

&lt;212&gt; PRT

10 &lt;213&gt; Homo sapiens

&lt;400&gt; 22

Met Ala Leu Val Pro Cys Gln Val Leu

1

5

15 Arg Met Ala Ile Leu Leu Ser Tyr Cys Ser Ile Leu Cys Asn Tyr Lys

10 15 20 25

Ala Ile Glu Met Pro Ser His Gln Thr Tyr Gly Gly Ser Trp Lys Phe

30 35 40

Leu Thr Phe Ile Asp Leu Val Ile Gln Ala Val Phe Phe Gly Ile Cys

20 45 50 55

Val Leu Thr Asp Leu Ser Ser Leu Leu Thr Arg Gly Ser Gly Asn Gln

60 65 70

Glu Gln Glu Arg Gln Leu Lys Lys Leu Ile Ser Leu Arg Asp Trp Met

75 80 85

25 Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val Phe

90 95 100 105

Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu Leu

110 115 120

Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr Val

30 125 130 135

Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr Pro

140 145 150

20/45

Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly Tyr  
 155 160 165  
 Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val Tyr  
 170 175 180 185  
 5 Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe Gly  
 190 195 200  
 Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val Leu  
 205 210 215  
 Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys Glu  
 10 220 225 230  
 Lys Pro Lys Leu Glu  
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 15 <211> 1168  
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 Met Ala Asp Pro Leu Arg Glu Arg Thr Glu Leu Leu Leu Ala  
 1 5 10  
 gac tac ctg ggg tac tgc gcc cgg gaa ccc ggc acc ccc gag ccg gcg 96  
 Asp Tyr Leu Gly Tyr Cys Ala Arg Glu Pro Gly Thr Pro Glu Pro Ala  
 25 15 20 25 30  
 cca tcc acg ccc gag gcc gcc gtg ctg cgc tcc gcg gcc gcc agg tta 144  
 Pro Ser Thr Pro Glu Ala Ala Val Leu Arg Ser Ala Ala Ala Arg Leu  
 35 40 45  
 cgg cag att cac cgg tcc ttt ttc tcc gcc tac ctc ggc tac ccc ggg 192  
 30 Arg Gln Ile His Arg Ser Phe Phe Ser Ala Tyr Leu Gly Tyr Pro Gly  
 50 55 60  
 aac cgc ttc gag ctg gtg gcg ctg atg gcg gat tcc gtg ctc tcc gac 240

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Asn Arg Phe Glu Leu Val Ala Leu Met Ala Asp Ser Val Leu Ser Asp  
 65 70 75  
 agc ccc gcc ccc acc tgg gcc aga gtg gtg acg ctc gtg acc ttc gca 288  
 Ser Pro Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala  
 5 80 85 90  
 ggg acg ctg ctg gag aga ggg ccg ctg gtg acc gcc cgg tgg aag aag 336  
 Gly Thr Leu Leu Glu Arg Gly Pro Leu Val Thr Ala Arg Trp Lys Lys  
 95 100 105 110  
 tgg gcc ttc cag ccg cgg cta aag gag cag gag gcc gac gtc gcc cgg 384  
 10 Trp Gly Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg  
 115 120 125  
 gac tgc cag cgc ctg gtg gcc ttg ctg agc tcg cgg ctc atg ggg cag 432  
 Asp Cys Gln Arg Leu Val Ala Leu Leu Ser Ser Arg Leu Met Gly Gln  
 130 135 140  
 15 cac cgc gcc tgg ctg cag gct cag gcc gcc tgg gat gcc ttt tgt cac 480  
 His Arg Ala Trp Leu Gln Ala Gln Gly Gly Trp Asp Gly Phe Cys His  
 145 150 155  
 ttc ttc agg acc ccc ttt cca ctg gct ttt tgg aga aaa cag ctg gtc 528  
 Phe Phe Arg Thr Pro Phe Pro Leu Ala Phe Trp Arg Lys Gln Leu Val  
 20 160 165 170  
 cag gct ttt ctg tca tgc ttg tta aca aca gcc ttc att tat ctc tgg 576  
 Gln Ala Phe Leu Ser Cys Leu Leu Thr Thr Ala Phe Ile Tyr Leu Trp  
 175 180 185 190  
 aca cga tta tta tgagttttaa aacttttaac ccgcttctac ctgcccaact gt 630  
 25 Thr Arg Leu Leu  
 gaccaactaa atgacagatg tgtgagaaca agaactgagg gaaagcacct tccccaccc 690  
 cagacgtttt tacctgaatg catacaagga gtccctgaggt ggtgatttgg ccagtgtttt 750  
 aacttgtagac aagtactcag gtgtgaggac aagaatgcaa atggctcttc cttgagtga 810  
 30 agaaatgggg agtctagagc ctctttatgc caaagaaccg cagaagaaac tgcattccat 870  
 taaatgggaa atacagtgtc atttgctaaa acttgataa gagtgcgaac ctctcatctc 930  
 tccacaactt catgtgtctc tgactaattt taaacatggc cacagctggg gcaaaataat 990

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ccccaaagta gaaaaagtcc cagtttaaca aagaatgtaa tgttaaaatc acttataagg 1050  
aattctttga aaccaaatcc ttgaaatct aattcctggg acttctaggt ttttatagtt 1110  
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<212> PRT  
<213> Homo sapiens

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Asp Tyr Leu Gly Tyr Cys Ala Arg Glu Pro Gly Thr Pro Glu Pro Ala  
15 20 25 30  
15 Pro Ser Thr Pro Glu Ala Ala Val Leu Arg Ser Ala Ala Ala Arg Leu  
35 40 45  
Arg Gln Ile His Arg Ser Phe Phe Ser Ala Tyr Leu Gly Tyr Pro Gly  
50 55 60  
Asn Arg Phe Glu Leu Val Ala Leu Met Ala Asp Ser Val Leu Ser Asp  
20 65 70 75  
Ser Pro Gly Pro Thr Trp Gly Arg Val Val Thr Leu Val Thr Phe Ala  
80 85 90  
Gly Thr Leu Leu Glu Arg Gly Pro Leu Val Thr Ala Arg Trp Lys Lys  
95 100 105 110  
25 Trp Gly Phe Gln Pro Arg Leu Lys Glu Gln Glu Gly Asp Val Ala Arg  
115 120 125  
Asp Cys Gln Arg Leu Val Ala Leu Leu Ser Ser Arg Leu Met Gly Gln  
130 135 140  
His Arg Ala Trp Leu Gln Ala Gln Gly Gly Trp Asp Gly Phe Cys His  
30 145 150 155  
Phe Phe Arg Thr Pro Phe Pro Leu Ala Phe Trp Arg Lys Gln Leu Val  
160 165 170

23/45

Gln Ala Phe Leu Ser Cys Leu Leu Thr Thr Ala Phe Ile Tyr Leu Trp

175 180 185 190

Thr Arg Leu Leu

5 &lt;210&gt; 25

&lt;211&gt; 624

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

10 &lt;400&gt; 25

tttgacggaa ggagcggcgg cgacggagga ggagg atg gag gcg gtg gtg ttc 53

Met Glu Ala Val Val Phe

1 5

gtc ttc tct ctc ctc gat tgt tgc gcg ctc atc ttc ctc tcg gtc tac 101

15 Val Phe Ser Leu Leu Asp Cys Cys Ala Leu Ile Phe Leu Ser Val Tyr

10 15 20

ttc ata att aca ttg tct gat tta gaa tgt gat tac att aat gct aga 149

Phe Ile Ile Thr Leu Ser Asp Leu Glu Cys Asp Tyr Ile Asn Ala Arg

25 30 35

20 tca tgt tgc tca aaa tta aac aag tgg gta att cca gaa ttg att ggc 197

Ser Cys Cys Ser Lys Leu Asn Lys Trp Val Ile Pro Glu Leu Ile Gly

40 45 50

cat acc att gtc act gta tta ctg ctc atg tca ttg cac tgg ttc atc 245

His Thr Ile Val Thr Val Leu Leu Leu Met Ser Leu His Trp Phe Ile

25 55 60 65 70

ttc ctt ctc aac tta cct gtt gcc act tgg aat ata tat cga tac att 293

Phe Leu Leu Asn Leu Pro Val Ala Thr Trp Asn Ile Tyr Arg Tyr Ile

75 80 85

atg gtg ccg agt ggt aac atg gga gtg ttt gat cca aca gaa ata cac 341

30 Met Val Pro Ser Gly Asn Met Gly Val Phe Asp Pro Thr Glu Ile His

90 95 100

aat cga ggg cag ctg aag tca cac atg aaa gaa gcc atg atc aag ctt 389

24/45

Asn Arg Gly Gln Leu Lys Ser His Met Lys Glu Ala Met Ile Lys Leu  
           105                    110                    115  
 ggt ttc cac ttg ctc tgc ttc ttc atg tat ctt tat agt atg atc tta 437  
 Gly Phe His Leu Leu Cys Phe Phe Met Tyr Leu Tyr Ser Met Ile Leu  
 5           120                    125                    130  
 gct ttg ata aat gac tgaagctgga gaagccgtgg ttgaagtcag cctacact 490  
 Ala Leu Ile Asn Asp  
 135  
 acagtgcaca gttgaggagc cagagacttc ttaaatacatc cttagaaccg tgaccatagc 550  
 10 agtatatatt ttcctcttgg aacaaaaaac tattttttgct gtattttttac catataaagt 610  
 atttaaaaaa catg 624  
  
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 <213> Homo sapiens  
  
 <400> 26  
  
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                     10                    15                    20  
 Phe Ile Ile Thr Leu Ser Asp Leu Glu Cys Asp Tyr Ile Asn Ala Arg  
                     25                    30                    35  
 25 Ser Cys Cys Ser Lys Leu Asn Lys Trp Val Ile Pro Glu Leu Ile Gly  
                     40                    45                    50  
 His Thr Ile Val Thr Val Leu Leu Leu Met Ser Leu His Trp Phe Ile  
                     55                    60                    65                    70  
 Phe Leu Leu Asn Leu Pro Val Ala Thr Trp Asn Ile Tyr Arg Tyr Ile  
 30                      75                    80                    85  
 Met Val Pro Ser Gly Asn Met Gly Val Phe Asp Pro Thr Glu Ile His  
                     90                    95                    100

25/45

Asn Arg Gly Gln Leu Lys Ser His Met Lys Glu Ala Met Ile Lys Leu

105

110

115

Gly Phe His Leu Leu Cys Phe Phe Met Tyr Leu Tyr Ser Met Ile Leu

120

125

130

5 Ala Leu Ile Asn Asp

135

&lt;210&gt; 27

&lt;211&gt; 1121

10 &lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 24

gacagagggg aacaag atg gcg gcg ccg aag ggg agc ctc tgg gtg agg acc 52

15 Met Ala Ala Pro Lys Gly Ser Leu Trp Val Arg Thr

1

5

10

caa ctg ggg ctc ccg ccg ctg ctg ctg ctg acc atg gcc ttg gcc gga 100

Gln Leu Gly Leu Pro Pro Leu Leu Leu Leu Thr Met Ala Leu Ala Gly

15

20

25

20 ggt tcg ggg acc gct tcg gct gaa gca ttt gac tcg gtc ttg ggt gat 148

Gly Ser Gly Thr Ala Ser Ala Glu Ala Phe Asp Ser Val Leu Gly Asp

30

35

40

acg gcg tct tgc cac cgg gcc tgt cag ttg acc tac ccc ttg cac acc 196

Thr Ala Ser Cys His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr

25 45 50 55 60

tac cct aag gaa gag gag ttg tac gca tgt cag aga ggt tgc agg ctg 244

Tyr Pro Lys Glu Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu

65

70

75

ttt tca att tgt cag ttt gtg gat gat gga att gac tta aat cga act 292

30 Phe Ser Ile Cys Gln Phe Val Asp Asp Gly Ile Asp Leu Asn Arg Thr

80

85

90

aaa ttg gaa tgt gaa tct gca tgt aca gaa gca tat tcc caa tct gat 340

26/45

Lys Leu Glu Cys Glu Ser Ala Cys Thr Glu Ala Tyr Ser Gln Ser Asp  
           95                                  100                                  105  
 gag caa tat gct tgc cat ctt ggt tgc cag aat cag ctg cca ttc gct 388  
 Glu Gln Tyr Ala Cys His Leu Gly Cys Gln Asn Gln Leu Pro Phe Ala  
 5           110                                  115                                  120  
 gaa ctg aga caa gaa caa ctt atg tcc ctg atg cca aaa atg cac cta 436  
 Glu Leu Arg Gln Glu Gln Leu Met Ser Leu Met Pro Lys Met His Leu  
 125                                  130                                  135                                  140  
 ctc ttt cct cta act ctg gtg agg tca ttc tgg agt gac atg atg gac 484  
 10 Leu Phe Pro Leu Thr Leu Val Arg Ser Phe Trp Ser Asp Met Met Asp  
                                   145                                  150                                  155  
 tcc gca cag agc ttc ata acc tct tca tgg act ttt tat ctt caa gcc 532  
 Ser Ala Gln Ser Phe Ile Thr Ser Ser Trp Thr Phe Tyr Leu Gln Ala  
                                   160                                  165                                  170  
 15 gat gac gga aaa ata gtt ata ttc cag tct aag cca gaa atc cag tac 580  
 Asp Asp Gly Lys Ile Val Ile Phe Gln Ser Lys Pro Glu Ile Gln Tyr  
                                   175                                  180                                  185  
 gca cca cat ttg gag cag gag cct aca aat ttg aga gaa tca tct cta 628  
 Ala Pro His Leu Glu Gln Glu Pro Thr Asn Leu Arg Glu Ser Ser Leu  
 20           190                                  195                                  200  
 agc aaa atg tcc tat ctg caa atg aga aat tca caa gcg cac agg aat 676  
 Ser Lys Met Ser Tyr Leu Gln Met Arg Asn Ser Gln Ala His Arg Asn  
 205                                  210                                  215                                  220  
 ttt ctt gaa gat gga gaa agt gat ggc ttt tta aga tgc ctc tct ctt 724  
 25 Phe Leu Glu Asp Gly Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu  
                                   225                                  230                                  235  
 aac tct ggg tgg att tta act aca act ctt gtc ctc tcg gtg atg gta 772  
 Asn Ser Gly Trp Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val  
                                   240                                  245                                  250  
 30 ttg ctt tgg att tgt tgt gca act gtt gct aca gct gtg gag cag tat 820  
 Leu Leu Trp Ile Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr  
                                   255                                  260                                  265

27/45

gtt ccc tct gag aag ctg agt atc tat ggt gac ttg gag ttt atg aat 868  
 Val Pro Ser Glu Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn  
 270 275 280  
 gaa caa aag cta aac aga tat cca gct tct tct ctt gtg gtt gtt aga 916  
 5 Glu Gln Lys Leu Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg  
 285 290 295 300  
 tct aaa act gaa gat cat gaa gaa gca ggg cct cta cct aca aaa gtg 964  
 Ser Lys Thr Glu Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys Val  
 305 310 315  
 10 aat ctt gct cat tct gaa att taagcatttt tcttttaaaa gacaa 1010  
 Asn Leu Ala His Ser Glu Ile  
 320  
 gtgtaataga catctaaaat tccactcctc atagagcttt taaaatgggt tcattggata 1070  
 taggccttaa gaaatcacta taaaatgcaa ataaagttaac tcaaattctgt g 1121  
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 Gln Leu Gly Leu Pro Pro Leu Leu Leu Leu Thr Met Ala Leu Ala Gly  
 25 15 20 25  
 Gly Ser Gly Thr Ala Ser Ala Glu Ala Phe Asp Ser Val Leu Gly Asp  
 30 35 40  
 Thr Ala Ser Cys His Arg Ala Cys Gln Leu Thr Tyr Pro Leu His Thr  
 45 50 55 60  
 30 Tyr Pro Lys Glu Glu Glu Leu Tyr Ala Cys Gln Arg Gly Cys Arg Leu  
 65 70 75  
 Phe Ser Ile Cys Gln Phe Val Asp Asp Gly Ile Asp Leu Asn Arg Thr

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	80	85	90
	Lys Leu Glu Cys Glu Ser Ala Cys Thr Glu Ala Tyr Ser Gln Ser Asp		
	95	100	105
	Glu Gln Tyr Ala Cys His Leu Gly Cys Gln Asn Gln Leu Pro Phe Ala		
5	110	115	120
	Glu Leu Arg Gln Glu Gln Leu Met Ser Leu Met Pro Lys Met His Leu		
	125	130	135 140
	Leu Phe Pro Leu Thr Leu Val Arg Ser Phe Trp Ser Asp Met Met Asp		
	145	150	155
10	Ser Ala Gln Ser Phe Ile Thr Ser Ser Trp Thr Phe Tyr Leu Gln Ala		
	160	165	170
	Asp Asp Gly Lys Ile Val Ile Phe Gln Ser Lys Pro Glu Ile Gln Tyr		
	175	180	185
	Ala Pro His Leu Glu Gln Glu Pro Thr Asn Leu Arg Glu Ser Ser Leu		
15	190	195	200
	Ser Lys Met Ser Tyr Leu Gln Met Arg Asn Ser Gln Ala His Arg Asn		
	205	210	215 220
	Phe Leu Glu Asp Gly Glu Ser Asp Gly Phe Leu Arg Cys Leu Ser Leu		
	225	230	235
20	Asn Ser Gly Trp Ile Leu Thr Thr Thr Leu Val Leu Ser Val Met Val		
	240	245	250
	Leu Leu Trp Ile Cys Cys Ala Thr Val Ala Thr Ala Val Glu Gln Tyr		
	255	260	265
	Val Pro Ser Glu Lys Leu Ser Ile Tyr Gly Asp Leu Glu Phe Met Asn		
25	270	275	280
	Glu Gln Lys Leu Asn Arg Tyr Pro Ala Ser Ser Leu Val Val Val Arg		
	285	290	295 300
	Ser Lys Thr Glu Asp His Glu Glu Ala Gly Pro Leu Pro Thr Lys Val		
	305	310	315
30	Asn Leu Ala His Ser Glu Ile		
	320		

29/45

&lt;210&gt; 29

&lt;211&gt; 827

&lt;212&gt; DNA

5 &lt;213&gt; Homo sapiens

&lt;400&gt; 29

```

aacagcggcc ctgcggctgg cgcggcggac ggg atg agg cgc tgc agt ctc tgc      54
                                Met Arg Arg Cys Ser Leu Cys
10                                1                                5

gct ttc gac gcc gcc cgg ggg ccc agg cgg ctg atg cgt gtg ggc ctc      102
Ala Phe Asp Ala Ala Arg Gly Pro Arg Arg Leu Met Arg Val Gly Leu
                                10                                15                                20

gcg ctg atc ttg gtg ggc cac gtg aac ctg ctg ctg ggg gcc gtg ctg      150
15 Ala Leu Ile Leu Val Gly His Val Asn Leu Leu Leu Gly Ala Val Leu
                                25                                30                                35

cat ggc acc gtc ctg cgg cac gtg gcc aat ccc cgc ggc gct gtc acg      198
His Gly Thr Val Leu Arg His Val Ala Asn Pro Arg Gly Ala Val Thr
                                40                                45                                50                                55

ccg gag tac acc gta gcc aat gtc atc tct gtc ggc tcg ggg ctg ctg      246
20 Pro Glu Tyr Thr Val Ala Asn Val Ile Ser Val Gly Ser Gly Leu Leu
                                60                                65                                70

agc gtt tcc gtg gga ctt gtg gcc ctc ctg gcg tcc agg aac ctt ctt      294
Ser Val Ser Val Gly Leu Val Ala Leu Leu Ala Ser Arg Asn Leu Leu
25                                75                                80                                85

cgc cct cca ctg cac tgg gtc ctg ctg gca cta gct ctg gtg aac ctg      342
Arg Pro Pro Leu His Trp Val Leu Leu Ala Leu Ala Leu Val Asn Leu
                                90                                95                                100

ctc ttg tcc gtt gcc tgc tcc ctg ggc ctc ctt ctt gct gtg tca ctc      390
30 Leu Leu Ser Val Ala Cys Ser Leu Gly Leu Leu Leu Ala Val Ser Leu
                                105                                110                                115

act gtg gcc aac ggt ggc cgc cgc ctt att gct gac tgc cac cca gga      438

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30/45

Thr Val Ala Asn Gly Gly Arg Arg Leu Ile Ala Asp Cys His Pro Gly  
 120 125 130 135  
 ctg ctg gat cct ctg gta cca ctg gat gag ggg ccg gga cat act gac 486  
 Leu Leu Asp Pro Leu Val Pro Leu Asp Glu Gly Pro Gly His Thr Asp  
 5 140 145 150  
 tgc ccc ttt gac ccc aca aga atc tat gat aca gcc ttg gct ctc tgg 534  
 Cys Pro Phe Asp Pro Thr Arg Ile Tyr Asp Thr Ala Leu Ala Leu Trp  
 155 160 165  
 atc cct tct ttg ctc atg tct gca ggg gag gct gct cta tct ggt tac 582  
 10 Ile Pro Ser Leu Leu Met Ser Ala Gly Glu Ala Ala Leu Ser Gly Tyr  
 170 175 180  
 tgc tgt gtg gct gca ctc act cta cgt gga gtt ggg ccc tgc agg aag 630  
 Cys Cys Val Ala Ala Leu Thr Leu Arg Gly Val Gly Pro Cys Arg Lys  
 185 190 195  
 15 gac gga ctt cag ggg cag gta gta gct ggg tgt gac gca aga gtg aaa 678  
 Asp Gly Leu Gln Gly Gln Val Val Ala Gly Cys Asp Ala Arg Val Lys  
 200 205 210 215  
 cag aaa gcc tgg cag cca cgg ttt cct ggg att aaa gtc aaa gca tta 726  
 Gln Lys Ala Trp Gln Pro Arg Phe Pro Gly Ile Lys Val Lys Ala Leu  
 20 220 225 230  
 tgaa tatggcacta aagtgactga gctaccagac caatgatcct gtaaggcagc 780  
 cacagaacta aaaaacaaca attattatta aactgctctg gattctc 827  
  
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 25 <211> 231  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 30  
 30 Met Arg Arg Cys Ser Leu Cys  
 1 5  
 Ala Phe Asp Ala Ala Arg Gly Pro Arg Arg Leu Met Arg Val Gly Leu

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	10	15	20
	Ala	Leu	Ile
	Leu	Val	Gly
	His	Val	Asn
	Leu	Leu	Leu
	Gly	Ala	Val
	Leu		
	25	30	35
	His	Gly	Thr
	Val	Leu	Arg
	His	Val	Ala
	Asn	Pro	Arg
	Gly	Ala	Val
	Thr		
5	40	45	50
	Pro	Glu	Tyr
	Thr	Val	Ala
	Asn	Val	Ile
	Ser	Val	Gly
	Ser	Gly	Leu
	Leu		
	60	65	70
	Ser	Val	Ser
	Val	Gly	Leu
	Val	Ala	Leu
	Leu	Ala	Ser
	Arg	Asn	Leu
	Leu		
	75	80	85
10	Arg	Pro	Pro
	Leu	His	Trp
	Val	Leu	Leu
	Ala	Leu	Ala
	Leu	Val	Asn
	Leu		
	90	95	100
	Leu	Leu	Ser
	Val	Ala	Cys
	Ser	Leu	Gly
	Leu	Leu	Leu
	Ala	Val	Ser
	Leu		
	105	110	115
	Thr	Val	Ala
	Asn	Gly	Gly
	Arg	Arg	Leu
	Ile	Ala	Asp
	Cys	His	Pro
	Gly		
15	120	125	130
	Leu	Leu	Asp
	Pro	Leu	Val
	Pro	Leu	Asp
	Glu	Gly	Pro
	Gly	His	Thr
	Asp		
	140	145	150
	Cys	Pro	Phe
	Asp	Pro	Thr
	Arg	Ile	Tyr
	Asp	Thr	Ala
	Leu	Ala	Leu
	Trp		
	155	160	165
20	Ile	Pro	Ser
	Leu	Leu	Met
	Ser	Ala	Gly
	Glu	Ala	Ala
	Leu	Ser	Gly
	Tyr		
	170	175	180
	Cys	Cys	Val
	Ala	Ala	Leu
	Thr	Leu	Arg
	Gly	Val	Gly
	Pro	Cys	Arg
	Lys		
	185	190	195
	Asp	Gly	Leu
	Gln	Gly	Gln
	Val	Val	Ala
	Gly	Cys	Asp
	Ala	Arg	Val
	Lys		
25	200	205	210
	Gln	Lys	Ala
	Trp	Gln	Pro
	Arg	Phe	Pro
	Gly	Ile	Lys
	Val	Lys	Ala
	Leu		
	220	225	230

&lt;210&gt; 31

30 &lt;211&gt; 1189

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

32/45

&lt;400&gt; 31

gtcgcctccc ggtcccggcc cggctactgc gctgcgccca ctccgctctg gagcctgggc 60  
 gcgggtcctg accttcccgg ccctctcctg acacctgggt gatggcgctca ccagaactcc 120  
 5 tagctgtgga accctagggc acctgttacc gcgctttggc gaaactgggt tcgctgctga 180  
 tttgcgaacc tttgcctgac tttctcaggc cttgagagat ctaagtaaatt ttgggtggccc 240  
 attgaaagga cctggagaga gcgtatgaag atctgcctct tctccaagaa actcaaccac 300  
 tagtgaca atg acc agc ctc ctg act act cct tct cca aga gaa gaa ctg 350  
 Met Thr Ser Leu Leu Thr Thr Pro Ser Pro Arg Glu Glu Leu  
 10 1 5 10  
 atg acc acc cca att tta cag ccc act gag gcc ctg tcc cca gaa gat 398  
 Met Thr Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp  
 15 20 25 30  
 gga gcc agc aca gca ctc att gca gtt gtt atc acc gtt gtc ttc ctc 446  
 15 Gly Ala Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu  
 35 40 45  
 acc ctg ctc tcg gtc gtg atc ttg atc ttc ttt tac ctg tac aag aac 494  
 Thr Leu Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn  
 50 55 60  
 20 aaa ggc agc tac gtc acc tat gaa cct aca gaa ggt gag ccc agt gcc 542  
 Lys Gly Ser Tyr Val Thr Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala  
 65 70 75  
 atc gtc cag atg gag agt gac ttg gcc aag ggc agc gag aaa gag gaa 590  
 Ile Val Gln Met Glu Ser Asp Leu Ala Lys Gly Ser Glu Lys Glu Glu  
 25 80 85 90  
 tat ttc atc taatgactcc caggcccaaa ggagcttatt cctggctcca t 640  
 Tyr Phe Ile  
 95  
 cgctaacacg ttgactgctt attatgggaa agttttctct gaagccaggg agaagcattg 700  
 30 attgatgtgg gcaaatacaa gctccagcca ggtgcagtc ccaaatgccg acatcactga 760  
 ctccagggac cagggaatg gagaaagctg tttatgatat ctttaaccag gccctottac 820  
 tagagctggg gtttgtgact ggccaacaag atgtggctat gccaggggac atctgagtat 880

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gtgcccagtc atcttttttc acaggttgaa gggagagaaa agattttgag ttaaggteat 940  
 tggctgctct actctgtccc ctacctggtc acctagtgat agccccagtg gagatactgt 1000  
 ccatacaagg tcttcccaga ggcctggatac cacagtaaaa ggccaggcca ggaggggtag 1060  
 gagactatgg agatcttacc tcctgataaa tgtgctacac cccctaattct gagcccttcc 1120  
 5 tttccgtgtt ccccaacaac ctcatgetta cgtgattttt attcaaatta aaaattttca 1180  
 ttgctacag 1189

&lt;210&gt; 32

&lt;211&gt; 97

10 &lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 32

Met Thr Ser Leu Leu Thr Thr Pro Ser Pro Arg Glu Glu Leu  
 15 1 5 10  
 Met Thr Thr Pro Ile Leu Gln Pro Thr Glu Ala Leu Ser Pro Glu Asp  
 15 20 25 30  
 Gly Ala Ser Thr Ala Leu Ile Ala Val Val Ile Thr Val Val Phe Leu  
 35 40 45  
 20 Thr Leu Leu Ser Val Val Ile Leu Ile Phe Phe Tyr Leu Tyr Lys Asn  
 50 55 60  
 Lys Gly Ser Tyr Val Thr Tyr Glu Pro Thr Glu Gly Glu Pro Ser Ala  
 65 70 75  
 Ile Val Gln Met Glu Ser Asp Leu Ala Lys Gly Ser Glu Lys Glu Glu  
 25 80 85 90  
 Tyr Phe Ile  
 95

&lt;210&gt; 33

30 &lt;211&gt; 1500

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

34/45

&lt;400&gt; 33

	ctgtgcctga gectgagcct gagcctgagc ctgagcccga gccgggagcc ggtcgcgggg	60
	gctccggggct gtgggaccgc tgggccccca gcg atg gcg acc ctg tgg gga ggc	114
5	Met Ala Thr Leu Trp Gly Gly	
	1 5	
	ctt ctt egg ctt ggc tcc ttg ctc agc ctg tcg tgc ctg gcg ctt tcc	162
	Leu Leu Arg Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser	
	10 15 20	
10	gtg ctg ctg ctg gcg cag ctg tca gac gcc gcc aag aat ttc gag gat	210
	Val Leu Leu Leu Ala Gln Leu Ser Asp Ala Ala Lys Asn Phe Glu Asp	
	25 30 35	
	gtc aga tgt aaa tgt atc tgc cct ccc tat aaa gaa aat tct ggg cat	258
	Val Arg Cys Lys Cys Ile Cys Pro Pro Tyr Lys Glu Asn Ser Gly His	
15	40 45 50 55	
	att tat aat aag aac ata tct cag aaa gat tgt gat tgc ctt cat gtt	306
	Ile Tyr Asn Lys Asn Ile Ser Gln Lys Asp Cys Asp Cys Leu His Val	
	60 65 70	
	gtg gag ccc atg cct gtg egg ggg cct gat gta gaa gca tac tgt cta	354
20	Val Glu Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu	
	75 80 85	
	cgc tgt gaa tgc aaa tat gaa gaa aga agc tct gtc aca atc aag gtt	402
	Arg Cys Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val	
	90 95 100	
25	acc att ata att tat ctc tcc att ttg ggc ctt cta ctt ctg tac atg	450
	Thr Ile Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Leu Tyr Met	
	105 110 115	
	gta tat ctt act ctg gtt gag ccc ata ctg aag agg cgc ctc ttt gga	498
	Val Tyr Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly	
30	120 125 130 135	
	cat gca cag ttg ata cag agt gat gat gat att ggg gat cac cag cct	546
	His Ala Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro	

35/45

	140	145	150	
	ttt gca aat gca cac gat gtg cta gcc cgc tcc cgc agt cga gcc aac			594
	Phe Ala Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn			
	155	160	165	
5	gtg ctg aac aag gta gaa tat gca cag cag cgc tgg aag ctt caa gtc			642
	Val Leu Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val			
	170	175	180	
	caa gag cag cga aag tct gtc ttt gac cgg cat gtt gtc ctc agc			687
	Gln Glu Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser			
10	185	190	195	
	taattgggaa ttgaattcaa ggtgactaga aagaaacagg cagacaactg gaa			740
	agaactgact gggttttgtt gggtttcatt ttaatacctt gttgatttca ccaactgttg			800
	ctggaagatt caaaactgga agcaaaaact tgcttgattt ttttttcttg ttaacgtaat			860
	aatagagaca tttttaaaag cacacagctc aaagtcagcc aataagtctt ttcctatttg			920
15	tgacttttac taataaaaat aaatctgcct gttaaattatc ttgaagtccct ttacctggaa			980
	caagcactct ctttttcacc acatagtttt aacttgactt tcaagataat tttcagggtt			1040
	tttggtgttg ttgttttttg tttgtttggt ttggtgggag aggggagggg tgccctgggaa			1100
	gtggttaaca acttttttca agtcacttta ctaaacaac ttttgtaaat agaccttacc			1160
	ttctattttc gagtttcatt tatattttgc agtgtagcca gcctcatcaa agagctgact			1220
20	tactcatttg acttttgcaac tgactgtatt atctgggtat ctgotgtgtc tgcacttcat			1280
	ggtaaacggg atctaaaatg cctggtggct tttcacaaaa agcagatttt cttcatgtac			1340
	tgtgatgtct gatgcaatgc atcctagaac aaactggcca tttgetagtt tactctaaag			1400
	actaaacata gtcttggtgt gtgtggtctt actcatcttc tagtaccttt aaggacaaat			1460
	cctaaggact tggacacttg caataaagaa attttatttt			1500
25				
	<210> 34			
	<211> 198			
	<212> PRT			
	<213> Homo sapiens			
30				
	<400> 34			

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Met Ala Thr Leu Trp Gly Gly  
1 5  
Leu Leu Arg Leu Gly Ser Leu Leu Ser Leu Ser Cys Leu Ala Leu Ser  
10 15 20  
5 Val Leu Leu Leu Ala Gln Leu Ser Asp Ala Ala Lys Asn Phe Glu Asp  
25 30 35  
Val Arg Cys Lys Cys Ile Cys Pro Pro Tyr Lys Glu Asn Ser Gly His  
40 45 50 55  
Ile Tyr Asn Lys Asn Ile Ser Gln Lys Asp Cys Asp Cys Leu His Val  
10 60 65 70  
Val Glu Pro Met Pro Val Arg Gly Pro Asp Val Glu Ala Tyr Cys Leu  
75 80 85  
Arg Cys Glu Cys Lys Tyr Glu Glu Arg Ser Ser Val Thr Ile Lys Val  
90 95 100  
15 Thr Ile Ile Ile Tyr Leu Ser Ile Leu Gly Leu Leu Leu Tyr Met  
105 110 115  
Val Tyr Leu Thr Leu Val Glu Pro Ile Leu Lys Arg Arg Leu Phe Gly  
120 125 130 135  
His Ala Gln Leu Ile Gln Ser Asp Asp Asp Ile Gly Asp His Gln Pro  
20 140 145 150  
Phe Ala Asn Ala His Asp Val Leu Ala Arg Ser Arg Ser Arg Ala Asn  
155 160 165  
Val Leu Asn Lys Val Glu Tyr Ala Gln Gln Arg Trp Lys Leu Gln Val  
170 175 180  
25 Gln Glu Gln Arg Lys Ser Val Phe Asp Arg His Val Val Leu Ser  
185 190 195

&lt;210&gt; 35

&lt;211&gt; 806

30 &lt;212&gt; DNA

&lt;213&gt; Homo sapiens

37/45

&lt;400&gt; 35

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gttcgtctag atttgtcggc ttgcggggag acttcaggag tcgctgtctc tgaacttcca      60
gcctcagaga ccgcgcgcct tgccccgag ggcc atg ggc cgg gtc tca ggg ctt      115
                                     Met Gly Arg Val Ser Gly Leu

5                                     1                                     5

gtg ccc tct cgc ttc ctg acg ctc ctg gcg cat ctg gtg gtc gtc atc      163
Val Pro Ser Arg Phe Leu Thr Leu Leu Ala His Leu Val Val Val Ile
          10                      15                      20

acc tta ttc tgg tcc cgg gac agc aac ata cag gcc tgc ctg cct ctc      211
10 Thr Leu Phe Trp Ser Arg Asp Ser Asn Ile Gln Ala Cys Leu Pro Leu
          25                      30                      35

acg ttc acc ccc gag gag tat gac aag cag gac att cag ctg gtg gcc      259
Thr Phe Thr Pro Glu Glu Tyr Asp Lys Gln Asp Ile Gln Leu Val Ala
          40                      45                      50                      55

15 gcg ctc tct gtc acc ctg ggc ctc ttt gca gtg gag ctg gcc ggt ttc      307
Ala Leu Ser Val Thr Leu Gly Leu Phe Ala Val Glu Leu Ala Gly Phe
          60                      65                      70

ctc tca gga gtc tcc atg ttc aac agc acc cag agc ctc atc tcc att      355
Leu Ser Gly Val Ser Met Phe Asn Ser Thr Gln Ser Leu Ile Ser Ile

20          75                      80                      85

ggg gct cac tgt agt gca tcc gtg gcc ctg tcc ttc ttc ata ttc gag      403
Gly Ala His Cys Ser Ala Ser Val Ala Leu Ser Phe Phe Ile Phe Glu
          90                      95                      100

cgt tgg gag tgc act acg tat tgg tac att ttt gtc ttc tgc agt gcc      451
25 Arg Trp Glu Cys Thr Thr Tyr Trp Tyr Ile Phe Val Phe Cys Ser Ala
          105                      110                      115

ctt cca gct gtc act gaa atg gct tta ttc gtc acc gtc ttt ggg ctg      499
Leu Pro Ala Val Thr Glu Met Ala Leu Phe Val Thr Val Phe Gly Leu
          120                      125                      130                      135

30 aaa aag aaa ccc ttc tgattacctt catgaaggga acctaaggac gaagcc      550
Lys Lys Lys Pro Phe
          140

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tacaggggca agggccgctt cgtattcctg gaagaaggaa ggcataaggct tcggttttcc 610  
 cctcggaaac tgcttctget ggaggatatg tgttggaata attacgtctt gagtctggga 670  
 ttatccgcat tgtatttagt gctttgtaat aaaatatgtt ttgtagtaac attaagactt 730  
 atatacagtt ttaggggaca attgagatgg ctgaactact gaataaaaaa aaaacaacgc 790  
 5 tgttttctag tctctg 806

&lt;210&gt; 36

&lt;211&gt; 140

&lt;212&gt; PRT

10 &lt;213&gt; Homo sapiens

&lt;400&gt; 36

Met Gly Arg Val Ser Gly Leu

1

5

15 Val Pro Ser Arg Phe Leu Thr Leu Leu Ala His Leu Val Val Val Ile

10

15

20

Thr Leu Phe Trp Ser Arg Asp Ser Asn Ile Gln Ala Cys Leu Pro Leu

25

30

35

Thr Phe Thr Pro Glu Glu Tyr Asp Lys Gln Asp Ile Gln Leu Val Ala

20

40

45

50

55

Ala Leu Ser Val Thr Leu Gly Leu Phe Ala Val Glu Leu Ala Gly Phe

60

65

70

Leu Ser Gly Val Ser Met Phe Asn Ser Thr Gln Ser Leu Ile Ser Ile

75

80

85

25

Gly Ala His Cys Ser Ala Ser Val Ala Leu Ser Phe Phe Ile Phe Glu

90

95

100

Arg Trp Glu Cys Thr Thr Tyr Trp Tyr Ile Phe Val Phe Cys Ser Ala

105

110

115

Leu Pro Ala Val Thr Glu Met Ala Leu Phe Val Thr Val Phe Gly Leu

30

120

125

130

135

Lys Lys Lys Pro Phe

140

39/45

&lt;210&gt; 37

&lt;211&gt; 1718

&lt;212&gt; DNA

5 &lt;213&gt; Homo sapiens

&lt;400&gt; 37

	ttgtcctgac c atg aat agg acc aac gtc aat gtc ttt tct gag ctt tcc	50
	Met Asn Arg Thr Asn Val Asn Val Phe Ser Glu Leu Ser	
10	1 5 10	
	gct cct cgt cgc aat gaa gac ttt gtc etc ctg etc acc tac gtc etc	98
	Ala Pro Arg Arg Asn Glu Asp Phe Val Leu Leu Leu Thr Tyr Val Leu	
	15 20 25	
	ttc ttg atg gcg ctg acc ttc etc atg tcc tcc ttc acc ttc tgt ggt	146
15	Phe Leu Met Ala Leu Thr Phe Leu Met Ser Ser Phe Thr Phe Cys Gly	
	30 35 40 45	
	tcc ttc acg ggc tgg aag aga cat ggg gcc cac atc tac etc acg atg	194
	Ser Phe Thr Gly Trp Lys Arg His Gly Ala His Ile Tyr Leu Thr Met	
	50 55 60	
20	etc etc tcc att gcc atc tgg gtg gcc tgg atc acc ctg etc atg ctt	242
	Leu Leu Ser Ile Ala Ile Trp Val Ala Trp Ile Thr Leu Leu Met Leu	
	65 70 75	
	cct gac ttt gac cgc agg tgg gat gac acc atc etc agc tcc gcc ttg	290
	Pro Asp Phe Asp Arg Arg Trp Asp Asp Thr Ile Leu Ser Ser Ala Leu	
25	80 85 90	
	gct gcc aat ggc tgg gtg ttc ctg ttg gct tat gtt agt ccc gag ttt	338
	Ala Ala Asn Gly Trp Val Phe Leu Leu Ala Tyr Val Ser Pro Glu Phe	
	95 100 105	
	tgg ctg etc aca aag caa cga aac ccc atg gat tat cct gtt gag gat	386
30	Trp Leu Leu Thr Lys Gln Arg Asn Pro Met Asp Tyr Pro Val Glu Asp	
	110 115 120 125	
	gct ttc tgt aaa cct caa etc gtg aag aag agc tat ggt gtg gag aac	434

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Ala Phe Cys Lys Pro Gln Leu Val Lys Lys Ser Tyr Gly Val Glu Asn

130 135 140

aga gcc tac tct caa gag gaa atc act caa ggt ttt gaa gag aca ggg 482

Arg Ala Tyr Ser Gln Glu Glu Ile Thr Gln Gly Phe Glu Glu Thr Gly

5 145 150 155

gac acg ctc tat gcc ccc tat tcc aca cat ttt cag ctg cag aac cag 530

Asp Thr Leu Tyr Ala Pro Tyr Ser Thr His Phe Gln Leu Gln Asn Gln

160 165 170

cct ccc caa aag gaa ttc tcc atc cca cgg gcc cac gct tgg ccg agc 578

10 Pro Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser

175 180 185

cct tac aaa gac tat gaa gta aag aaa gag ggc agc taactctgtc ctgaag 630

Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser

190 195 200

15 agtgggacaa atgcagccgg ggggcagatc tagcgggagc tcaaagggat gtgggcgaaa 690

tcttgagtct tctgagaaaa ctgtacaaga cactacggga acagtttgcc tccctcccag 750

cctcaaccac aattcttcca tgctggggct gatgtgggct agtaagactc cagttottag 810

agggcgtgta gtattttttt tttttttgtc tcctccttag gatacttctt ttaagtggga 870

gtctcaggca actcaagttt agacccttac tctttttgtt tgttttttga aacaggatct 930

20 tgctctgtca cccaggett ggtgcagtgg tgcgatcaca gcccagtga gcctcgacca 990

cctgtgtca agcaatctc ccatctccat ctcccaaagt gctgggatga caggcgtgag 1050

ccacagctcc cagcctaggc ccttaattctt gctgttattt tccatggact aaaggtctgg 1110

tcctctgagc tcacgctggc tcacacagct ctaggggcct gctcctctaa ctcacagtgg 1170

gttttgtgag gctctgtggc ccagagcaga cctgcatatc tgagcaaaaa tagcaaaagc 1230

25 ctctctcagc ccactggcct gaactctacac tggaagccaa cttgctggca cccccgtcc 1290

ccaaccctc ttgcctgggt aggagagget aaagatcacc ctaaatttac tcctctctct 1350

agtgtgcct cacaactggc ctcagcagct cccagcacc aattcacagg tcaccctct 1410

cttcttgca tgtccccaaa cttgctgtca attccgagat ctaactctcc cctacgtct 1470

gccaggaatt ctttcagacc tcactagcac aagcccggtt gctccttgct aggagaattt 1530

30 gtacatcatt ctcacttcaa attcctgggg ctgatacttc totcatcttg caccccaacc 1590

tctgtaaata gatttaccgc atttacgget gcattctgta agtgggcatg gtctcctaatt 1650

ggaggagtgt tcattgtata ataagttatt cacctgagta tgcaataaag atgtggtggc 1710

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cactotttt

1718

&lt;210&gt; 38

&lt;211&gt; 201

5 &lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 38

	Met	Asn	Arg	Thr	Asn	Val	Asn	Val	Phe	Ser	Glu	Leu	Ser
10	1				5					10			
	Ala	Pro	Arg	Arg	Asn	Glu	Asp	Phe	Val	Leu	Leu	Leu	Thr
	15				20					25			
	Phe	Leu	Met	Ala	Leu	Thr	Phe	Leu	Met	Ser	Ser	Phe	Thr
	30				35					40			45
15	Ser	Phe	Thr	Gly	Trp	Lys	Arg	His	Gly	Ala	His	Ile	Tyr
				50					55				60
	Leu	Leu	Ser	Ile	Ala	Ile	Trp	Val	Ala	Trp	Ile	Thr	Leu
				65					70				75
	Pro	Asp	Phe	Asp	Arg	Arg	Trp	Asp	Asp	Thr	Ile	Leu	Ser
20		80					85					90	
	Ala	Ala	Asn	Gly	Trp	Val	Phe	Leu	Leu	Ala	Tyr	Val	Ser
		95					100					105	
	Trp	Leu	Leu	Thr	Lys	Gln	Arg	Asn	Pro	Met	Asp	Tyr	Pro
	110				115					120			125
25	Ala	Phe	Cys	Lys	Pro	Gln	Leu	Val	Lys	Lys	Ser	Tyr	Gly
				130						135			140
	Arg	Ala	Tyr	Ser	Gln	Glu	Glu	Ile	Thr	Gln	Gly	Phe	Glu
				145					150				155
	Asp	Thr	Leu	Tyr	Ala	Pro	Tyr	Ser	Thr	His	Phe	Gln	Leu
30		160					165					170	
	Pro	Pro	Gln	Lys	Glu	Phe	Ser	Ile	Pro	Arg	Ala	His	Ala
				175					180				185

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Pro Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser

190

195

200

&lt;210&gt; 39

5 &lt;211&gt; 995

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 39

10 agagctgggt gcgccgagcc ccctgcgcgc tgcacatggg gcgcctgacg gaagcggcgg 60  
 cagcggggcag cggtcttcgg gctgcaggct gggcagggtc ccctcccacg ctcttgccgc 120  
 tgtctcccac gtccccccagg tgcgcggcca cc atg gcg tcc agc gac gag gac 173  
 Met Ala Ser Ser Asp Glu Asp

15 ggc acc aac ggc ggc gcc tcg gag gcc ggc gag gac cgg gag gct ccc 221  
 Gly Thr Asn Gly Gly Ala Ser Glu Ala Gly Glu Asp Arg Glu Ala Pro

20 ggc aag cgg agg cgc ctg ggg ttc ttg gcc acc gcc tgg ctc acc ttc 269  
 Gly Lys Arg Arg Arg Leu Gly Phe Leu Ala Thr Ala Trp Leu Thr Phe

25 tac gac atc gcc atg acc gcg ggg tgg ttg gtt cta gct att gcc atg 317  
 Tyr Asp Ile Ala Met Thr Ala Gly Trp Leu Val Leu Ala Ile Ala Met

30 gta cgt ttt tat atg gaa aaa gga aca cac aga ggt tta tat aaa agt 365  
 Val Arg Phe Tyr Met Glu Lys Gly Thr His Arg Gly Leu Tyr Lys Ser

att cag aag aca ctt aaa ttt ttc cag aca ttt gcc ttg ctt gag ata 413  
 Ile Gln Lys Thr Leu Lys Phe Phe Gln Thr Phe Ala Leu Leu Glu Ile

gtt cac tgt tta att gga att gta cct act tct gtg att gtg act ggg 461  
 Val His Cys Leu Ile Gly Ile Val Pro Thr Ser Val Ile Val Thr Gly

90 95 100

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gtc caa gtg agt tca aga atc ttt atg gtg tgg ctc att act cac agt 509  
 Val Gln Val Ser Ser Arg Ile Phe Met Val Trp Leu Ile Thr His Ser  
 105 110 115  
 ata aaa cca atc cag aat gaa gag agt gtg gtg ctt ttt ctg gtc gcg 557  
 5 Ile Lys Pro Ile Gln Asn Glu Glu Ser Val Val Leu Phe Leu Val Ala  
 120 125 130 135  
 tgg act gtg aca gag atc act cgc tat tcc ttc tac aca ttc agc ctt 605  
 Trp Thr Val Thr Glu Ile Thr Arg Tyr Ser Phe Tyr Thr Phe Ser Leu  
 140 145 150  
 10 ctt gac cac ttg cca tac ttc att aaa tgg gcc aga tat aat ttt ttt 653  
 Leu Asp His Leu Pro Tyr Phe Ile Lys Trp Ala Arg Tyr Asn Phe Phe  
 155 160 165  
 atc atc tta tat cct gtt gga gtt gct ggt gaa ctt ctt aca ata tac 701  
 Ile Ile Leu Tyr Pro Val Gly Val Ala Gly Glu Leu Leu Thr Ile Tyr  
 15 170 175 180  
 gct gcc ttg ccg cat gtg aag aaa aca gga atg ttt tca ata aga ctt 749  
 Ala Ala Leu Pro His Val Lys Lys Thr Gly Met Phe Ser Ile Arg Leu  
 185 190 195  
 cct aac aaa tac aat gtc tct ttt gac tac tat tat ttt ctt ctt ata 797  
 20 Pro Asn Lys Tyr Asn Val Ser Phe Asp Tyr Tyr Tyr Phe Leu Leu Ile  
 200 205 210 215  
 acc atg gca tca tat ata cct ttg ttt cca caa ctc tat ttt cat atg 845  
 Thr Met Ala Ser Tyr Ile Pro Leu Phe Pro Gln Leu Tyr Phe His Met  
 220 225 230  
 25 tta cgt caa aga aga aag gtg ctt cat gga gag gtg att gta gaa aag 893  
 Leu Arg Gln Arg Arg Lys Val Leu His Gly Glu Val Ile Val Glu Lys  
 235 240 245  
 gat gat taaatgatct ctgcaaacaa ggtgcttttt ccagaataac caagattacc t 950  
 Asp Asp  
 30 gagtccaagt ttaataaca agaataaaca actttgtgaa atatc 995

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&lt;210&gt; 40

&lt;211&gt; 249

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

5

&lt;400&gt; 40

Met Ala Ser Ser Asp Glu Asp

1

5

10 Gly Thr Asn Gly Gly Ala Ser Glu Ala Gly Glu Asp Arg Glu Ala Pro  
10 15 20

Gly Lys Arg Arg Arg Leu Gly Phe Leu Ala Thr Ala Trp Leu Thr Phe  
25 30 35

Tyr Asp Ile Ala Met Thr Ala Gly Trp Leu Val Leu Ala Ile Ala Met  
40 45 50 55

15 Val Arg Phe Tyr Met Glu Lys Gly Thr His Arg Gly Leu Tyr Lys Ser  
60 65 70

Ile Gln Lys Thr Leu Lys Phe Phe Gln Thr Phe Ala Leu Leu Glu Ile  
75 80 85

20 Val His Cys Leu Ile Gly Ile Val Pro Thr Ser Val Ile Val Thr Gly  
90 95 100

Val Gln Val Ser Ser Arg Ile Phe Met Val Trp Leu Ile Thr His Ser  
105 110 115

Ile Lys Pro Ile Gln Asn Glu Glu Ser Val Val Leu Phe Leu Val Ala  
120 125 130 135

25 Trp Thr Val Thr Glu Ile Thr Arg Tyr Ser Phe Tyr Thr Phe Ser Leu  
140 145 150

Leu Asp His Leu Pro Tyr Phe Ile Lys Trp Ala Arg Tyr Asn Phe Phe  
155 160 165

30 Ile Ile Leu Tyr Pro Val Gly Val Ala Gly Glu Leu Leu Thr Ile Tyr  
170 175 180

Ala Ala Leu Pro His Val Lys Lys Thr Gly Met Phe Ser Ile Arg Leu  
185 190 195

45/45

Pro Asn Lys Tyr Asn Val Ser Phe Asp Tyr Tyr Tyr Phe Leu Leu Ile  
200 205 210 215  
Thr Met Ala Ser Tyr Ile Pro Leu Phe Pro Gln Leu Tyr Phe His Met  
220 225 230  
5 Leu Arg Gln Arg Arg Lys Val Leu His Gly Glu Val Ile Val Glu Lys  
235 240 245  
Asp Asp





## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C12N 15/12, C07K 14/705, C12N 5/10</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 00/00506</b> <b>(43) International Publication Date:</b> 6 January 2000 (06.01.00)
<b>(21) International Application Number:</b> PCT/JP99/03242 <b>(22) International Filing Date:</b> 18 June 1999 (18.06.99) <b>(30) Priority Data:</b> 10/180008 26 June 1998 (26.06.98) JP <b>(71) Applicants (for all designated States except US):</b> SAGAMI CHEMICAL RESEARCH CENTER [JP/JP]; 4-1, Nishi-Ohnuma 4-chome, Sagamihara-shi, Kanagawa 229-0012 (JP). PROTEGENE INC. [JP/JP]; 2-20-3, Naka-cho., Meguro-ku, Tokyo 153-0065 (JP). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> KATO, Seishi [JP/JP]; 3-46-50, Wakamatsu, Sagamihara-shi, Kanagawa 229-0014 (JP). KIMURA, Tomoko [JP/JP]; 302, 4-1-28, Nishiikuta, Tama-ku, Kawasaki-shi, Kanagawa 214-0037 (JP). <b>(74) Agents:</b> AOYAMA, Tamotsu et al.; Aoyama & Partners, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 540-0001 (JP).	<b>(81) Designated States:</b> AU, CA, JP, MX, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). <b>Published</b> <i>With international search report.</i> <b>(88) Date of publication of the international search report:</b> 20 April 2000 (20.04.00)	
<b>(54) Title:</b> HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAS ENCODING THESE PROTEINS <b>(57) Abstract</b> <p>A human protein having a hydrophobic domain and comprising any of the amino acid sequences represented by Sequence Nos. 1 to 10, a cDNA coding for said protein, and an expression vector comprising the cDNA as well as an eucaryotic cell comprising the cDNA. The protein can be provided by expression of the cDNA coding for such protein.</p>		

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# INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/JP 99/03242

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/705 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 21328 A (KATO SEISHI ;PROTEGENE INC (JP); SEKINE SHINGO (JP); SAGAMI CHEM R) 22 May 1998 see abstract see page 17, last paragraph - page 18, paragraph 1 --- -/--	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

20 October 1999

Date of mailing of the international search report

18. 02. 2000

Name and mailing address of the ISA

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Authorized officer

Lejeune, R

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 99/03242

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL Accession Number N94214, 19 April 1996 HILLIER L ET AL: "za27c03.r1 Homo sapiens cDNA clone 293764 5' similar to PIR:A54313 androgen-regulated protein FAR-17 - golden hamster" XP002119529 cited in the application 97.8% identity in 357 BP overlap with SEQ ID 11 see page 17, last paragraph - page 18, paragraph 1</p>	1-6
A	<p>--- D'ANDREA ET AL: "Molecular Cloning of NKB1. A Natural Killer Cell Receptor for HLA -B Allotypes" JOURNAL OF IMMUNOLOGY, vol. 155, no. 5, 1 September 1995, pages 2306-2310 2310, XP002111500 see abstract paragraph 1 see page 2307, right-hand column, line 16 - paragraph 1</p>	1-6
A	<p>--- GILLEN C M ET AL: "Molecular cloning and functional expression of the K-Cl cotransporter from rabbit, rat, and human." JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 271, no. 27, 5 July 1996, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US, pages 16237-16244, XP002119528 see abstract paragraph 1</p>	1-6
A	<p>--- KYTE J ET AL: "A SIMPLE METHOD FOR DISPLAYING THE HYDROPATHIC CHARACTER OF A PROTEIN" JOURNAL OF MOLECULAR BIOLOGY, vol. 157, no. 1, 5 May 1982, pages 105-132, XP000609692 cited in the application see the whole document paragraph 1</p>	1-6
P,X	<p>--- DATABASE EMBL Accession Number AF151861, 1 June 1999 LIN C W: "Homo sapiens CGI-103 protein mRNA, complete cds." XP002119530 99.4% identity in 699 BP overlap with SEQ ID 11 see the whole document paragraph 1</p> <p>--- -/--</p>	1-6

# INTERNATIONAL SEARCH REPORT

Internat Application No  
PCT/JP 99/03242

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>DATABASE EMBL Accession Number AF153605, 30 June 1999 KIM M K ET AL: "Homo sapiens androgen induced protein (AIG-1) mRNA, complete cds." XP002119531 99.7% identity in 714 BP overlap with SEQ ID NO 11 see the whole document paragraph 1 -----</p>	1-6

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 99/03242

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6 (partially), see additional sheet, subject 1.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-6 partially

A protein comprising the amino acid sequence SEQ ID NO 1, a DNA SEQ ID NO 11 or 21, encoding this protein, as well as an expression vector capable of expressing this sequence and a eukaryotic cell expressing the DNA

2. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 2 and DNA SEQ ID 12 and 23

3. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 3 and DNA SEQ ID 13 and 25

4. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 4 and DNA SEQ ID 14 and 27

5. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 5 and DNA SEQ ID 15 and 29

6. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 6 and DNA SEQ ID 16 and 31

7. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 7 and DNA SEQ ID 17 and 33

8. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 8 and DNA SEQ ID 18 and 35

9. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 9 and DNA SEQ ID 19 and 37

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 10 and  
DNA SEQ ID 20 and 39

### Information on patent family members

PCT/JP 99/03242

Form PCT/ISA/210 (patent family annex) (July 1992)

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